Center of Functionally Integrative Neuroscience
& MIND*Lab*

ANNUAL REPORT 2015 & 2016

cognition
PET
statistics
data
tensor
dendrite
MR
physics
scanning
music
neuroanatomy

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Sharing knowledge
Head of the technical staff at CFIN, Torben Lund, sharing new ideas on analysing data at a CFIN meeting.
Photo: Michael Harder, AUH Foto

Introduction - 2015 & 2016 in words

by Leif Østergaard

This annual report, with its familiar layout and design by Henriette Blæsild Vuust, is the tenth sent out to colleagues, collaborators, and all those who support our work, to provide you with updates on our latest progress to understand the human brain and mind, and to find causes and cures for their diseases. Combating disease took on a personal dimension in early 2016, as Henriette endured strenuous cancer therapy. We depend on Henriette's creative touch for many aspects of CFIN/MIND*Lab*'s work – and an annual report without her would simply not be 'the real deal'. Reports concerning our 2015 activities are therefore part of this year's one-off, biannual CFIN/MIND*Lab* report. We are grateful that Henriette now made a full recovery, set to inspire annual reports and our center's communication for many years to come.

In the summer of 2015, the Danish National Research Foundation's Center for Music in the Brain (MIB) was inaugurated. Thanks to the Central Denmark Regions decision to establish the Danish Neuroscience Center (DNC) in 2009, CFIN/MIND*Lab* can continue to share office space, meeting rooms and infrastructure with our new 'sister center' at the fourth and fifth floors of the DNC building, as MIB enters a phase of rapid growth. We continue to enjoy the cross-fertilization that occurs as neuroimaging, basic and clinical neuroscience fuse with studies of music, cognition, and behavior – during scientific as well as social gatherings.

In 2016, neuroscientist and electrophysiology/MEG expert Sarang Dalal joined CFIN/MIND*Lab* from Konstanz University. Sarang Dalal is a European Research Council (ERC) Starting Grant recipient and with this funding, his Neuroelectromagnetic Oscillations Laboratory (NEMOlab) will study interactions between the retina and the visual cortex.

Over the past few years, CFIN/MIND*Lab* has undergone a gradual transition, both in terms of its funding and its organization. While many of our researchers and their work used to be organized according to research themes that were part of large center-grants, the CFIN/MIND*Lab* 'family' is now comprised of many research groups which collaborate closely, but maintain their own focus, funding, and leadership. Today, these research groups represent the tangible legacy after the large investments made by the Danish National Research Foundation to establish CFIN and the Danish Governments UNIK initiative to establish MIND*Lab*. The researchers share office space, administrative resources, and, importantly, our experimental infrastructure, which was established with grants from the Danish Research Agency's Infrastructure program, the VILLUM and VELUX Foundations, and our host institutions. With this equipment, the methods we develop, and the know-how our researchers have developed over the past two decades, we are well positioned to turn our ideas into grants, even when public research investments are dwindling, and to attract talents and future research leaders to our groups.

The least tangible, but perhaps most important, legacy of the CFIN and MIND*Lab* center grants is the level of collaboration between groups: I'm proud and delighted to see the extent to which CFIN/MIND*Lab* researchers share knowledge, know-how and ideas, helping each other to succeed. Having cultivated multi-, inter-, cross-, trans- and postdisciplinary collaborations for over 15 years, we have learned to exercise curiosity, respect, and humility, both as we work with fellow researchers, irrespective of their educational background and seniority – and as we try to unravel nature's secrets from the many ways they present themselves to neuroscientists. For research groups in a complex and multifaceted research area such as ours, being generous with one's time and resources – and reciprocating the generosity of others – is a strong recipe for scientific progress, and for a productive and friendly working environment.

As CFIN/MIND*Lab* continues to grow, so does our need for space and for new tools to realize the potential of our ideas. With the Nørrebrogade branch of Aarhus University Hospital set to move to Skejby in 2019, we look forward to expand our clinical research in new buildings, closer to clinical researchers from other medical specialties. Meanwhile, the number of CFIN/MIND*Lab* employees in need of office space has grown considerably since the hospital went through its initial planning stages – much unlike its budget. Having relocated numerous times since we first set up shop in a basement lunch-room, we hope to find more permanent homes in the coming year. Meanwhile, CFIN/MIND*Lab* researchers have developed concepts and tools which may change the way we prevent, diagnose, and treat major diseases. To translate these breakthroughs into better patient management, we currently seek to expand our experimental infrastructure to include cutting-edge scanners which will allow us to make more precise diagnoses, as well as new therapeutic strategies available to patients during their admission. Read more about these and other efforts on the following pages!

Once again, on behalf of the CFIN/MIND*Lab* leadership, I wish to thank you for your continued interest, support, and collaboration

Leif Østergaard
CFIN / MIND*Lab* director

NEUROPHYSICS 2015-2016

by Ahmad R. Khan, Brian Hansen and Sune Nørhøj Jespersen

MRI is a core neuroimaging modality in clinical and preclinical settings, capable of generating a plethora of contrasts reflecting a wide range of tissue properties. Diffusion-weighted MRI, in particular, is known to be sensitive to biological structure on the scale of micrometers, i.e. the size of cells and far exceeding the nominal imaging resolution of MRI. By providing a noninvasive window into tissue microstructure, diffusion MRI has the potential to detect subtle tissue changes associated with disease at very early stages, promising improved opportunities for intervention. While its sensitivity among noninvasive imaging modalities is unparalleled, improving specificity to individual and clinically relevant tissue properties is a major research focus. To interpret diffusion MRI data accurately in terms of specific tissue alterations, adequate biophysical modelling of diffusion MRI combined with independent and quantitative histological validation is indispensable, and a main focus of the neurophysics group at CFIN.

In 2015-2016 we made progress in terms of rapid whole brain imaging of crucial diffusion MRI parameters, fast imaging of kurtosis and neurite density, validation of new diffusion schemes for the detection of microscopic fractional anisotropy, new methods for quantitative 3-D histology, and applications of some of these technologies to fibrotic mouse kidneys and human gliomas. Meanwhile, we extended our work within physiological modeling, as PhD student Hugo Angleys published a paper in which he develops a model of the critical effects of capillary transit time heterogeneity in brain oxygenation, a phenomenon whose role we also investigated in functional activation and a number of diseases including diabetic neuropathy, cortical spreading depression, Alzheimer's disease, and critical illness. He also published a paper on the implications of capillary transit time heterogeneity on glucose extraction, oxygen glucose index.

All of the work in the group depends heavily on collaborations with other groups at CFIN.

Rapid imaging of kurtosis metrics

Most clinical studies analyse diffusion-weighted MRI in terms of the diffusion tensor and derived metrics, but it is well-known that a more complete description of the diffusion, with increased sensitivity to microstructure, is obtained by including the so-called kurtosis tensor, a measure of non-gaussian aspects of diffusion. A main obstacle so far has been the comprehensive data necessary to facilitate such an analysis, and to a smaller degree, a rather involved parameter estimation procedure. We discovered that careful selection of diffusion directions can reduce the number of required images to only 19 (compared to at least 60), which can be acquired in about 2 minutes, while maintaining a very accurate and robust estimation. The post processing procedure was also substantially simplified, and can be performed by linear operations in a few seconds for whole brain coverage (compared to hours for the conventional procedure). This work was selected as the Editor's pick for the November 2016 issue of Magnetic Resonance In Medicine, and followed up with an interview by MRM highlights and audio slides on the accompanying YouTube channel.

The method presented in the November MRM paper is potentially valuable for diagnostics outside of the brain, when pathology causes organ microstructure to change. One example is kidney fibrosis which often accompanies chronic kidney disease. Currently, the course of this disease is monitored using needle biopsies of the kidney. These

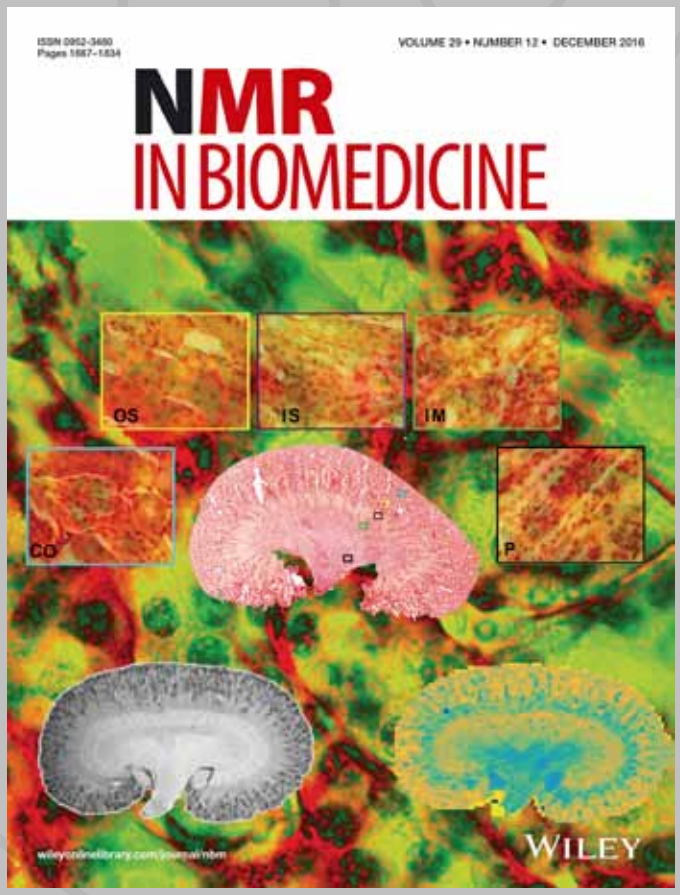


Figure 1
The cover of NMR in Biomedicine December 2016, from Kjølby et al NMR Biomed., 29(12), 1709-1719 (2016).

procedures are prone to errors due to imprecise sampling and do not cover the entire organ. In addition, a biopsy is invasive, and the risk of complications is therefore not negligible. A safe, non-invase scan sensitive to kidney fibrosis would therefore be an important clinical tool. In a recent publication, we demonstrate that our fast kurtosis technique is able to distinguish healthy and diseased mouse kidneys. Histology identifies fibrosis as the main cause of the difference in kurtosis parameters between the groups. We also propose an optimized protocol for fast kurtosis of human kidneys for clinical use. The paper is due to appear in NMR in Biomedicine and has been selected for the cover of its issue (December 2016).

Until recently, only mean kurtosis could be measured with the rapid kurtosis protocol. A further development in rapid kurtosis imaging was published in NeuroImage 2016, where we showed how to measure radial and axial kurtosis, two other kurtosis derived metrics that are widely reported to display increased sensitivity to microstructural tissue alterations. The method does not require additional data, but relies on novel analysis. Hence, with our technique for rapid kurtosis imaging, clinicians can now access all commonly reported kurtosis metrics with greatly reduced data demands and post processing. We believe this will facilitate further exploration of these promising kurtosis metrics by easing their inclusion in clinical studies.

Subtle microstructural alterations in depression

In 2015, we developed a quantitative histological analysis tool specifically to corroborate the diffusion MRI data. An ISMRM abstract based on automated histological analysis tool to validate the diffusion MRI data was picked for the ISMRM Magna Cum Laude merit award 2016 (see Figure 2).

One disease believed to cause subtle microstructural brain alterations, is depression. Depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease. However, to date depression is not diagnosed with objective tests, and no gross brain pathology has been reported. To explore microstructural alteration in stress sensitive regions of the brain, we have employed biophysical modelling of diffusion MRI data, kurtosis imaging and automated histological analysis to explore the microstructural alteration in chronic mild stress (CMS) rats, a model of depression. The MR based neurite density and mean tensor kurtosis (MKT) metrics have shown significantly

FACTS

Group members, students and collaborators:

- Sune N. Jespersen (group leader)
- Brian Hansen (head of high field lab)
- Ahmad Khan (post. doc.)
- Birgitte Fuglsang Kjølby (MR physicist)
- Andrey Chuhutin (PhD student)
- Hugo Angleys (PhD student)

Conferences and meetings:

- New Dimensions in Diffusion Encoding (January 2016, Sweden)
- Diffusion DeKay (April 2016, Aarhus, Denmark)
- ISMRM 2015 (May 2015, Toronto)
- ISMRM 2016 (May 2016, Singapore)
- Federation of all European Neuroscience Societies (FENS) (Copenhagen, 2016).
- Quantitive Susceptibility Mapping (September 2016, Graz, Austria)

Funding:

- Lundbeck Foundation (cellular underpinnings of diffusion weighted contrast)
- Simon Fougner Hartmans Familiefond
- Kornings fond
- VELUX Foundation
- ISMRM travel award (Ahmad Khan)

Invited talks:

- Ahmad Khan: Diffusion DeKay (Danish/Swedish diffusion MRI network)
- Sune Jespersen: EUROMAR (July 2016, Aarhus, Denmark), ISMRM (May 2016, Singapore), New Dimensions In Diffusion Encoding (January 2016, Bäckaskog Castle, Sweden), University College London (March 2016, Denmark).
- Brian Hansen: Bridging Nordic Imaging, Göteborg 14-15 April 2016

Activities:

- Teaching MR physics (Aarhus university School of Engineering, Sune Jespersen, Brian Hansen, Birgitte F. Kjølby), Advanced Magnetic Resonance Imaging (Sino Danish Center, Sune Jespersen & Andrey Chuhutin), electrodynamics (Department of Physics and Astronomy, Sune Jespersen & Hugo Angleys), Neurophysics (Department of Physics and Astronomy, Sune Jespersen), and Special Relativity (Department of Physics and Astronomy, Sune Jespersen).
- Educational talk in connection with “Lysets Dag” (commemorating Niels Bohrs birthday, Sune Jespersen).
- Brian Hansen visited Los Alamos National Lab’s Pulsed Field Facility as a member of the user committee for the National High Magnetic Field Lab.
- Training visit to Professor Donald Kuhn at Wayne State University, MI, USA. (Ahmad Khan)
- Outstanding teacher award ISMRM Singapore 2016, (Sune Jespersen)
- Conference organizer (Sune Jespersen): New Dimensions in Diffusion Encoding (Bäckaskog Castle, Sweden), Diffusion Dekay (April 2016, Aarhus, Denmark)
- PhD Opponent UCL (Sune N. Jespersen)
- Associate Professor Evaluation committee (Sune Jespersen, chairman)

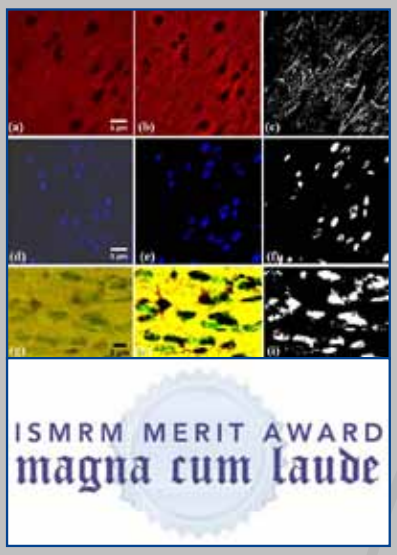


Figure 2
ISMRM Magna Cum Laude merit award 2016.
Chronic mild stress induces changes in neurite density in the amygdala as revealed by diffusion MRI and validated with novel histological analyses. Ahmad R. Khan, Andrey Chuhutin, Ove Wiborg, Christopher D. Kroenke, Jens R. Nyengaard, Brian Hansen, and Sune N. Jespersen.
Biophysical modelling of diffusion MRI data allows the detection of specific tissue characteristics such as neurite density. Although histological validation is cumbersome, this process remains crucial because it represents the gold standard in our efforts to develop a non-invasive "MR-microscope". The present study applies Matlab based image processing and analysis tools to compute histological neurite density to validate diffusion MRI based neurite density changes in the amygdala of chronic mild stress rat brains. The image processing and analyses provides novel tools to validate diffusion data robustly.

higher value in amygdala and histological neurite density also showed similar increase in amygdala of CMS rats. The finding is also supported by previously employed invasive techniques such as neuronal tracing and stereology in the chronic mild stress rat model. Diffusion MRI also demonstrated significant decrease in extracellular diffusivity in the amygdala, hippocampus, caudate and putamen of stressed rat brain. The results are consistent with an increased activity in the amygdala, a brain region involved in emotional reactions, such as fear. The hippocampus, on the other hand, plays an important role in learning, and its microstructural alterations indicate compromised function with potentially detrimental effects on the ability to assimilate new skills or knowledge. This work is published in NeuroImage and a Data in Brief article provides the data under a public repository.

In the same CMS study, we also observed diffusion MRI based alteration in auditory and motor cortex of CMS rats. The extracellular diffusivity in auditory cortex was significantly lower in of both the stressed group (resilient and anhedonic) while motor cortex showed significantly higher FA, only in the resilient group. This work was presented as an abstract at FENS 2016. Histological analysis is under way to support the diffusion MRI based finding.

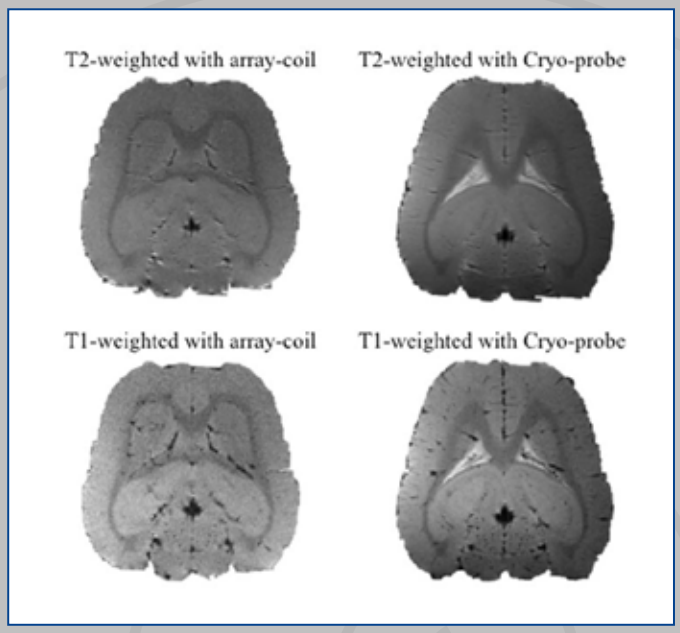


Figure 3
Direct comparison of image quality obtained with a traditional room temperature array coil (left column) and the newly acquired cryo probe (right column). The only difference between the images in each row is the hardware used. The cryo probe's superior image quality is evident in both scan types. The cryo probe improves the signal-to-noise ratio (SNR) by a factor of ~6 for the T2 scans and a factor of ~3 for the T1 scans. This exceeds the vendor specifications.

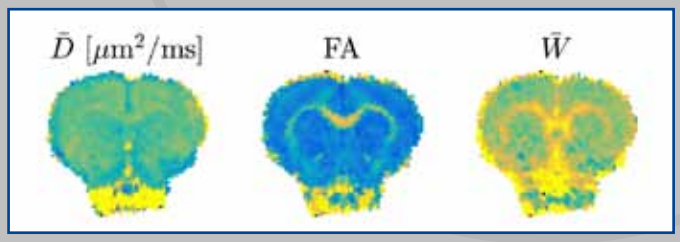


Figure 4
Example of fast kurtosis imaging in vivo using the cryoprobe (left to right: mean diffusivity, fractional anisotropy (FA), and mean tensor kurtosis (W). The mean kurtosis is a very promising microstructural marker in the brain and will be explored as a marker for microstructural remodeling following stress and repeated trauma (ongoing work).

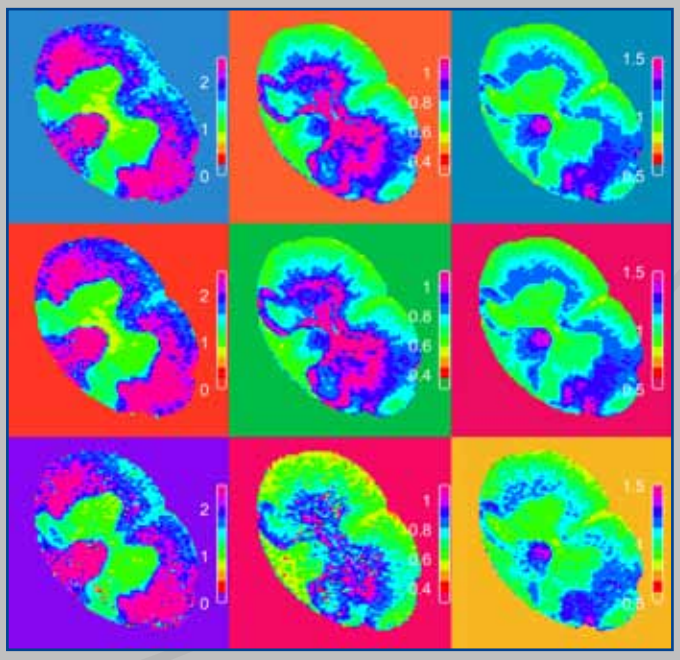
High Field Lab

In late 2015, CFIN's high field MRI lab was upgraded with one of the world's first rat brain cryocoils. This purchase was made possible by a generous donation from the VELUX Foundation. The cryocoil is a piece of hardware that improves image quality and measurement sensitivity immensely (see Figure 3 for examples and comparisons to our previous setup). This improvement is achieved by cooling the radio-frequency coil used for signal detection as well as the pre-amplifiers

associated with the coil. This reduces the electronic noise contamination in the measurements so that signal-to-noise is improved by up to a factor of 5-6 compared to conventional hardware. A similar increase in SNR through increased magnetic field strength would require a 54 T magnet which would be prohibitively expensive and in reality most likely unsuitable for imaging for technical reasons.

The cryocoil is currently being used for spectroscopy and microstructural imaging in the study of chronic mild stress and will also be used in an upcoming traumatic brain injury project. *In vivo* examples of diffusion weighted scans used for tissue microstructure imaging are provided in Figure 4. Measurements of this type and quality were not possible with our previous hardware setup.

Collaboration with other labs is an important part of establishing the high field MR-lab. In this context, the long time collaboration with Dr Jeremy Flint and Professor Stephen Blackband at the University of Florida remains crucial. A joint publication with this group (Flint, Hansen, Blackband, Sci. Rep. 2015 Dec 15;5:18095. doi: 10.1038/srep18095) was chosen for the National High Magnetic Field Lab's list of Best Research of 2015 (Biology section).
https://nationalmaglab.org/news-events/news/best-research-of-2015



Visual illustration of the fast kurtosis method for estimation of axial and radial kurtosis.
Our work uses axial scans of fixed rat spinal cord as a model system. With this slice orientation the spinal cord's familiar butterfly-shaped gray matter core is very evident. Columns show radial, axial, and mean kurtosis (left to right). The top row shows images obtained by conventional methods (general DKI fit). The middle row shows estimates obtained from an axially symmetric DKI fit using a large data set. Finally, the bottom row shows the parameter estimates obtained when fitting the axially symmetric model to a small fraction (a 1-9-9 subset) of the full data set. The parameter estimates we obtain with our novel method are so similar to the ground truth values that the figure looks like repetitions of the same row of images with only small variations. This reminded us of Andy Warhol's iconic Marilyn series (1962). For this reason we redid the figure with a color scheme resembling Warhol's bright colors in a triple triptych. The scientific content of the figure, however, is preserved, much in agreement with pop art's attention to fact and detail.

Hansen B, Shemesh N, Jespersen SN. Fast imaging of mean, axial and radial diffusion kurtosis. Neuroimage, 142: 381–93.
Warhol inspired illustration by Brian Hansen.

FACTS

Events:

In June 2015, Sune Jespersen defended his doctoral thesis (Dr. Med. Sc.) entitled "Diffusion Magnetic Resonance Imaging of Brain Tissue Microstructure". The defense was a great opportunity for interesting scientific discussions with the two opponents, professors Daniel Alexander (UCL) and Jens Jensen (Medical University of South Carolina), who are leading international experts on diffusion imaging and its relation to tissue microstructure.

Former Dean at HEALTH (AU), Allan Flyvbjerg (middle) after having presented doctoral certificates to two new doctors of medicine, June 2015. Sune Jespersen on the right.

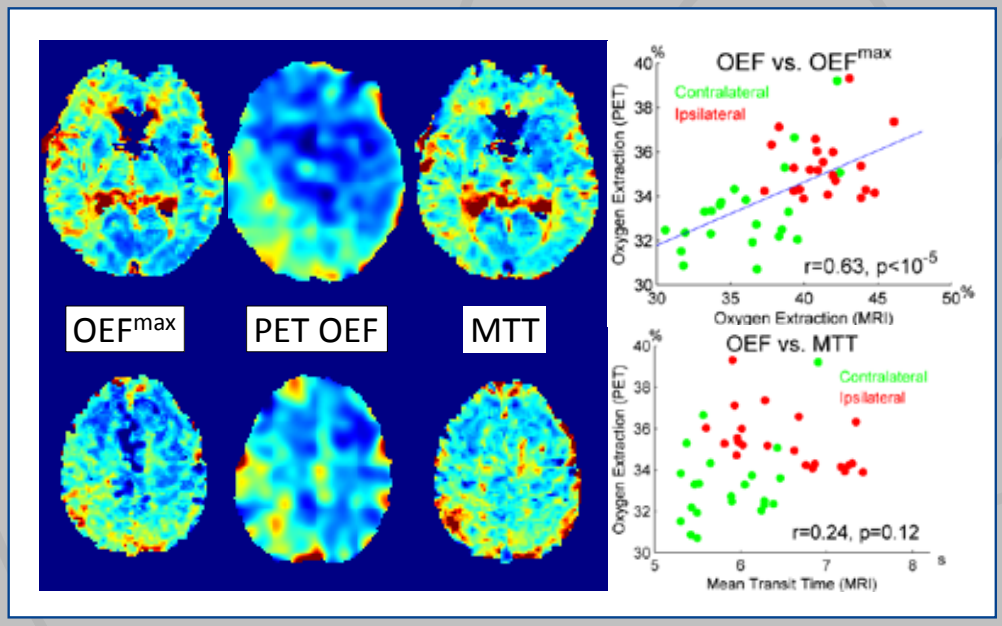
FUNCTIONAL HEMODYNAMICS

ARCADIA – Aarhus Research Center for Aging and Dementia

by Leif Østergaard

Funded by the VELUX Foundation, the functional hemodynamics group examines a fundamental theory on the relation between the function of the microcirculation on one hand, and the availability of oxygen and nutrients such as glucose in tissue, on the other. Based on century-old studies of single capillaries, the availability of oxygen in tissue has traditionally been inferred from its blood supply, which, in turn, is regulated to meet the metabolic needs of the tissue via flow-metabolic coupling mechanisms that regulate the diameter of feeding blood vessels.

Following a breakthrough in our ability to understand the role of the microcirculation published in 2012[1], we proposed that the availability of oxygen (and that other diffusible solutes) is really determined by the blood supply and its microscopic distribution. We further assumed that a range of mechanisms must protect tissue from drops in tissue levels of oxygen or any other substrate for cellular energy metabolism: Else, oxygen and energy depletion would be expected to activate inflammatory pathways and – if severe – cell dysfunction and death. As a result, flow-metabolism coupling cannot be fully understood without taking the efficacy of downstream oxygen extraction into account, and we hypothesized that capillaries may play a key role in sensing local oxygen tension and in regulating cellular-level blood supply and local capillary flow patterns to optimize oxygen extraction capacity. Notably, our models predicted that flow-metabolism coupling mechanisms may sometimes alter blood supply in unexpected manners in order to optimize tissue oxygen tension. Thus, slight reductions in oxygen extraction efficacy due to capillary flow disturbances can, in theory, be counteracted by increasing blood supply – giving rise to a paradox condition dubbed *mild capillary dysfunction* in which vascular risk factors give rise to elevated perfusion to maintain normal tissue oxygenation – so-called *pre-symptomatic hyperemia*. Needless to say, human subjects are rarely examined before they develop any symptoms. Nevertheless, while examining whether our theory could explain poorly understood aspects of disease pathophysiology, we have come across several cases of unexplained hyperemia in asymptomatic subjects: In college-age carriers of the APOE-ε4 gene, which has been associated with the development of late-onset Alzheimer's disease (AD) decades later, both resting cerebral blood flow (CBF) and CBF increases during functional activation are significantly larger than in age-matched controls[2]. Similarly, elevated blood flow has been observed in the nerve trunks of patients with type-2 diabetes prior to their development of signs of diabetic neuropathy[3]. Interestingly, in both cases,



Figure

This figure, reproduced from reference 11, shows PET and MR data from two patients with occlusion of their right carotid artery. Both had experienced short episodes of left-sided hemiparesis and right-sided amaurosis fugax (blindness), but experienced no neurological deficits at the time of the study. Occlusion of their carotid arteries was diagnosed by ultrasonic examination, and competing cerebral pathologies were excluded by earlier MRI. Their DSC MRI images and corresponding PET images were co-registered in order to display predicted oxygen extraction fraction (OEFmax) and actual, measured OEF based on the local uptake of radiolabeled oxygen and water (an indicator of blood supply), respectively by PET. The three panels on the left compares mean transit time (MTT, an indicator of blood supply) and OEFmax images, obtained by MRI, to OEF maps obtained by PET, at two slice locations in one of the patients. In the two plots to the right, the ability of MTT and OEFmax to predict "true" OEF is compared for the hemispheres ipsi- and contralateral to the stenosis (red and green dots) in 11 slices each of the two patients. The higher OEF in the affected side is traditionally ascribed to severe hypoperfusion caused by carotid stenosis. If this was exclusively so, the lower graph should reveal a linear relationship. It is, however, only when the microvascular distribution of flows is also taken into account (upper graph) that oxygen extraction can be accounted for, suggesting that both large vessel occlusion and capillary dysfunction contributed to the patients' symptoms.

findings of elevated blood flow have been taken as evidence that vascular disturbances could not contribute to AD or diabetic neuropathy, despite the abundance of vascular risk factors in the two conditions. With the support of the VELUX Foundation to Rasmus Aamand and of the Novo Nordisk Foundation to establish the International Diabetic Neuropathy Consortium (IDNC), these hypotheses are now being tested – See the 2014 Annual Report.

The theory, that tissue blood flow not only reflects the metabolic needs of the tissue but also the efficacy by which oxygen can be extracted from the microcirculation, has now lead to a series of testable hypotheses regarding the etiology of poorly understood diseases and disease mechanisms, published in a series of 11 manuscripts so far. In 2015-16, collaborations with national and international experts resulted in papers outlining the role of the microcirculation in cortical spreading depolarizations, an enigmatic phenomenon thought to provoke migraine auras and to contribute to tissue injury after brain injury[4]. Similarly, a thorough analysis revealed that capillary dysfunction seemingly play a key role in cerebral small vessel disease, a large and heterogeneous range of conditions which carry a high risk of both stroke and cognitive decline[5]. Careful scrutiny of our theory's ability to explain both known and poorly understood aspects of a range of diseases has represented a series of 'acid test' to our ideas. The theory now stands stronger than when we first started conceiving it, and our analyses have resulted in a number of striking, testable hypotheses which we and others, who read our articles, now test. If these studies verify that capillary dysfunction is involved in a range of diseases, these 'position'-studies define fundamentally new avenues in preventing, diagnosing, and managing major diseases. Unsurprisingly, our bold ideas have jokingly been dubbed 'The Theory of Everything' – out of equal amounts of well-placed skepticism and encouragement!

Needless to say, tests of our research hypotheses depend on the development of methods to characterize microvascular hemodynamics. Kim Mouridsen has developed a method that characterizes flow patterns within millimeter-sized magnetic resonance imaging (MRI) voxels in human brain, based on dynamic susceptibility contrast (DSC) MRI, which essentially captures the transit time characteristics of plasma as it passes though cerebral vessels[6,7]. The paper also reported intriguing changes in microvascular flow patterns in tissue severely affected by reduced blood supply after acute stroke in humans. PhD student Thorbjørn Søndergaard Engedal has

FACTS

Group members:

- Leif Østergaard
- Hugo Angleys
- Maryam Anzabi
- Eugenio Gutiérrez Jiménez
- Thorbjørn Søndergaard Engedal
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- Anete Dudele
- Tristan Hollyer
- Klaus Ulrik Koch
- Rune Bæksager
- Sune Nørhøj Jespersen
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- Peter Mondrup Rasmussen
- Simon Fristed Eskildsen
- Jakob Udby Blicher
- Arne Møller
- Kim Ryun Drasbek
- Rasmus Aamand Olesen
- Rikke Beese Dalby
- Nina Kerting Iversen
- Maryam Ardalen
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- Troels Staehelin Jensen, Nanna Brix Finnerup and Astrid J. Terkelsen, International Diabetic Neuropathy Consortium (IDNC), Danish Pain Research Center (DPRC), and Dept. Neurology, Aarhus University Hospital
- Jens Christian Hedemann Sørensen, Dept. Neurosurgery, Aarhus University Hospital
- Mads Rasmussen and Niels Juul, Division of Neuroanesthesiology, , Dept. Anesthesiology and Intensive Care, Aarhus University Hospital
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- David Boas, Sava Sakadzic, Baoqiang Lee, Optics Division, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard-MIT Health Sciences and Technology
- David Boas, Boston University College of Engineering
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- Timothy W. Secomb, Microcirculation Division, Arizona Research Laboratories, Department of Physiology and Mathematics, University of Arizona
- Axel Pries, Charité Universitätsmedizin Berlin, Department of Physiology, Berlin
- Amy F. Smith, Groupe d'Études sur les Milieux Poreux, Institute de Mécanique de Fluides de Toulouse, France
- Keith Muir, Fiona Moreton and Jozien Goense, Institute of Neuroscience and Psychology, University of Glasgow

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now studied this phenomenon in greater detail, submitting his thesis and three manuscripts on the subject in early 2017. Mikkel Bo Hansen published an extension of the DSC-MRI method in 2016, so that it now allows the characterization of flow patterns in diseases with contrast leakage, such as in patients with brain tumors[8]. The potential importance of capillary dysfunction and the accompanying tissue hypoxia in cancer was described in the 2014 annual report. Since then, these hypotheses have been confirmed and extended in brain tumors and peritumoral edema in studies conducted by Anna Tietze (see also page 12-15)[9] and a study with collaborators in Heidelberg[10]. Meanwhile, head-to-head comparisons of the MRI based method's predictions of oxygen extraction efficacy to gold-standard measurements by positon emission tomography (PET) confirm that capillary dysfunction can have important implications for the management of cerebrovascular diseases[11]: Accordingly, cerebral oxygen uptake is better accounted for when both blood supply and capillary flow patterns are taken into account, as compared to blood supply, as previously assumed – See Figure on page 8. Therapeutically, this implies that therapies, which target microvascular function, may provide additional benefits for patients who undergo surgical or interventional therapies to restore blood supply.

As part of his PhD project, Eugenio Gutiérrez-Jiménez utilized the indicator-dilution formalism developed for DSC MRI studies (above) in a modified version, so that he could derive capillary transport characteristics from arterial and venous fluorescein isothiocyanate (FITC) concentration time curves, measured directly in the cortical microvessels of mice by two-photon microscopy. He measured changes in blood flow and in the capillary distribution of blood during functional activation[12] as well as during hypercapnia[13]. Intriguingly, his results suggest that capillary flow patterns homogenize more than one would expect from the parallel changes in blood flow, suggesting that capillaries actively dilate in response to neural activation, facilitating the extraction of oxygen by what we dubbed neuro-capillary coupling mechanisms[1]. Indeed, recent studies show capillary pericytes dilate in response to glutamatergic neurotransmission, prior to the upstream vasodilation[14], and measurements by optical coherence tomography confirm that capillary flow patterns homogenize prior to the increase in flow[15], confirming that capillary flow patterns, and thus oxygen extraction efficacy, is actively regulated by neurocapillary coupling mechanisms. When comparing net oxygen extraction during normal conditions to those obtained during hypercapnia (as predicted from measurements of blood flow and its microscopic distribution) Eugenio Gutiérrez-Jiménez came to a striking conclusion: Although blood flow may increase by as much as 100-200% during hypercapnia, the modest, parallel changes in capillary flow patterns resulted in virtually unaltered oxygen availability[13]. Hypercapnia has traditionally been thought to cause an overabundance of oxygen while brain metabolism remains unaltered. These findings support the assumption that blood supply and oxygen extraction efficacy, combined, remain closely coupled to the metabolic needs of the tissue, even under such extreme physiological conditions (see also page 16-17).

In 2015, postdoc Peter Mondrup Rasmussen finalized a thorough study, aiming to examine whether changes in capillary flow patterns can help explain the observed relations between blood flow and blood/tissue oxygenation during functional activation. Previous models of oxygen transport in tissue could only explain such experimental data if capillary properties were allowed to vary in ways that lacked mechanistic or physiological underpinnings. Using a dynamic model of oxygen extraction to model epochs of functional activation and a realistic model of the microvasculature, Peter demonstrated that capillary flow patterns invariably homogenize as flow increases through passive compliant microvascular networks, improving oxygen extraction efficacy in a way that explains earlier experimental findings[16]. Since then, Peter Mondrup Rasmussen has devoted time to develop a framework for managing the enormous amounts of data that are usually recorded during studies of the microcirculation. Typically, thousands of observations of hematocrit, erythrocyte velocities or fluxes are collected across capillary segments which, in turn, are either interconnected, or connected to portions of the microvasculature which cannot be observed. Now, how do we best report such data to other scientists – for example in terms of a few, critical parameters? And how accurately did our experiment determine these parameters? And finally, do our models of blood flow through the microcirculation indeed explain our measurements with sufficient accuracy? This effort recently resulted in a comprehensive approach which will become a critical tool as scientists increasingly analyze and report measurements of the microcirculation[17].

Hugo Angleys started his PhD project by extending the original model of oxygen extraction across capillary networks developed by Sune Nørhøj Jespersen[1] in order to examine the effects of tissue metabolism and of the choice of capillary

transit time distributions on the original model predictions[18]. The resulting model indeed provides a more realistic model of oxygen extraction and oxygen tension differences in tissue, while confirming that capillary flow patterns have profound effects on oxygen extraction efficacy. Hugo Angleys then went on to determine the effects of capillary flow patterns on glucose extraction in tissue, comparing it to that of oxygen. While glucose transport into brain tissue proved less sensitive to capillary flow patterns than that of oxygen, this particular difference proved to offer an intriguing explanation to a decade-old enigma: The tendency of brain tissue to produce lactate during brain work, although oxygen supplies, as gleaned from the parallel increase in blood supply, seems sufficient. While some have suggested that that these findings reflect a preference of astrocytes to produce lactate, Hugo Angleys' study shows that the phenomenon can in fact be explained by the differential effects of capillary flow patterns on glucose and oxygen extraction during functional activation – such that oxygen is, in fact, not as available for ATP production during functional activation as previously assumed. Meanwhile, Hugo Angleys uncovered a plausible explanation to yet another paradox in the established literature on the brains glucose metabolism: Glucose metabolism has traditionally been measured indirectly, quantifying the accumulation of a labeled glucose-analog (typically fluor-labeled deoxyglucose, known as FDG) rather than glucose itself. The uptake of glucose is widely assumed to be proportional to that of the glucose analog, but Hugo Angleys' analysis shows that this assumption is in error when comparing uptake in, for example, the resting and activated brain. This error, in turn, leads to overestimations of the extent of glucose consumption relative to that of oxygen during functional activation. Indeed, correcting this error, these 'indirect' glucose uptake estimates showed better correspondence with results obtained by methods which detect glucose directly. Hugo Angleys is now addressing a critical aspect of capillary flow patterns, namely their effects on the blood oxygen level dependent (BOLD) contrast widely used in human brain mapping.

I wish to end this report on our progress by expressing my gratitude to the VELUX foundation for their financial support and to the researchers who produced these discoveries. My work with other senior group leaders, with our methods specialists and technical staff, and with the gifted, hardworking young talents I have the honor to work with, makes the unraveling of the microcirculation an exciting and joyful adventure!

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FUNCTIONAL HEMODYNAMICS

Advanced MRI methods in cerebral gliomas

by Anna Tietze

Brain tumors are divided into two large groups: Brain metastases are tumors that spread to the brain from a cancer disease in other parts of the body whereas primary brain tumors start to form in the brain. Gliomas are the most common malignant primary brain tumors and are characterized by their diffuse and infiltrative growth pattern. This property ultimately results in therapeutic failure, as individual glioma cells or small cell clusters tend to invade normal brain tissue, mimick normal brain cells and use pre-existing blood vessels to obtain oxygen and nutrients.

Gliomas are currently divided into their originating cell line with the most common being astrocytomas and oligodendrogliomas, and into different grades according to their malignancy[1]. Low-grade gliomas (LGG; grade I and II) are usually manageable for some years, but eventually progress into high-grade lesions (HGG; grade III and IV), as tumor cells commonly escape therapeutic approaches. The most aggressive glioma is the glioblastoma multiforme (GBM), which is the most common primary malignant brain tumor type and has a dismal prognosis of only about 27% of patients alive after two years. As LGGs slowly progress into HGGs, gliomas often show a characteristic heterogeneity with various cell clusters of different genotypic and phenotypic characteristics.

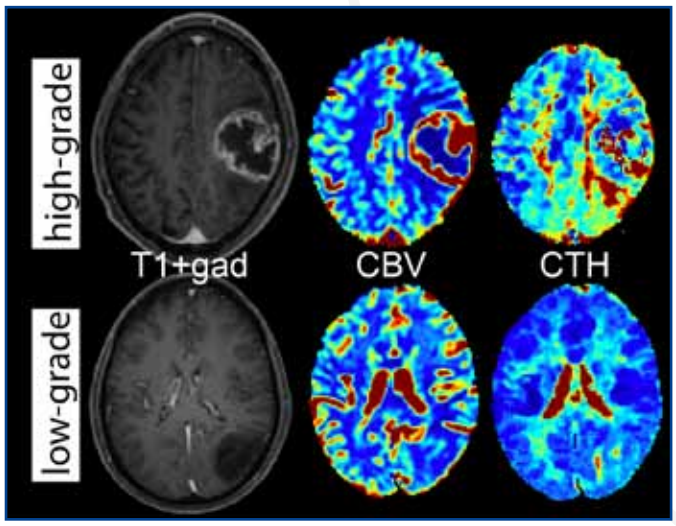

Figure 1
The high-grade glioma (upper row) shows increased Cerebral Blood Volume (CBV) in the contrast enhancing part of the tumor, whereas the capillary flow heterogeneity (CTH) is primarily high in the peri-focal region, indicating that CTH captures microvascular changes in the infiltrating part of the tumor. CBV and CTH are low in the low-grade glioma (lower row).

Magnetic Resonance Imaging (MRI) is the primary diagnostic tool in patients suspected for brain tumors. Imaging characteristics often guide radiologists and neurosurgeons with regard to the most likely diagnosis. Moreover, a detailed anatomical assessment is essential for the choice of the best therapeutical approach, be it the complete removal of the tumor or a biopsy, potentially combined with subsequent radiation and/or chemotherapy. Conventional MRI, however, underestimates the infiltrative growth and histological heterogeneity of gliomas, especially in the observational phase during radio-chemotherapy.

The aim of our studies was therefore to explore advanced MRI methods with regard to a more detailed evaluation of gliomas, their infiltrative growth pattern, and their expected biological behavior. We were particularly interested in MRI parameters to investigate the potential of tumors to develop new blood vessels (neo-angiogenesis) and to generate tissue hypoxia, both indicators for high malignancy. We also want to explore new MRI techniques to detect subtle microstructural changes, such as cellularity and micronecrosis. We particularly focused on MRI methods that are useful in a clinical setting, where critically ill patients cannot endure protracted imaging protocols, and where time constraints and the efficient use of health care resources are critical. In the following, I summarize the studies undertaken to address these questions:

In our first study, we used Dynamic Susceptibility Contrast (DSC) MRI to assess neo-angiogenesis and microvascular changes in gliomas, and we then correlated imaging biomarkers with tumor grade and patient outcome. In 72 patients, we compared the widely used Cerebral Blood Volume (CBV) maps with a newly developed parameter[2], the capillary transit time heterogeneity (CTH), which describes flow alterations that lead to tissue hypoxia. We found that CTH adds valuable diagnostic and prognostic information, and that the combination of CTH and the traditional angiogenesis marker CBV improves the ability to differentiate HGGs from LGGs (Figure 1). Most importantly, we showed that CTH, particularly when measured outside the tumor (as defined by conventional MRI) outperformed CBV in the prediction of disease progression and overall survival time (Figure 2). It is very likely that CTH, as an indirect indicator of tumor hypoxia, captures earlier stages of the disease, and we propose the CTH maps can be used clinically for biopsy guidance, outcome prediction, and therapy monitoring, especially during anti-angiogenic treatment[3].

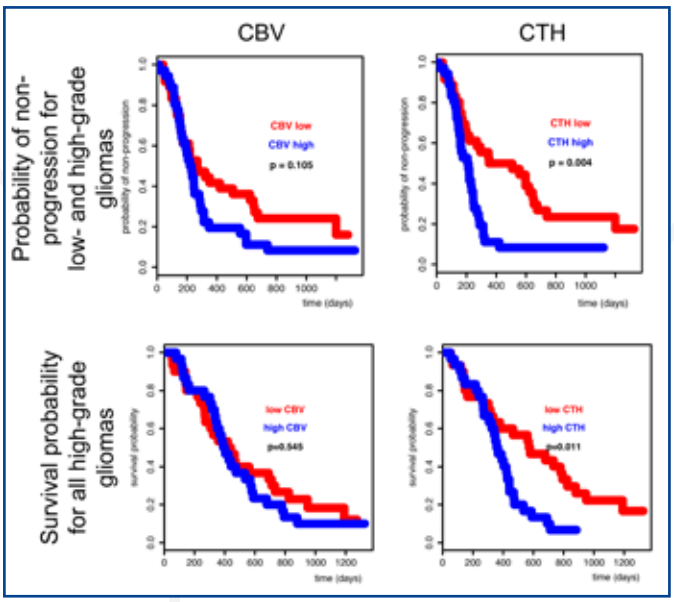

Figure 2
The capillary flow heterogeneity (CTH) appears to be a reliable ($p<0.05$) imaging biomarker for the time to disease progression in glioma patients (upper row), whereas CBV is not statistically significant ($p>0.05$). Moreover, CTH is a predictor for overall survival in patients with high-grade gliomas (lower row).

The second study explored the importance of accurate brain tissue T1-value measurements in Dynamic Contrast Enhanced (DCE) MRI, a technique that plays an increasing role in treatment monitoring. The quantitative evaluation of hemodynamic parameters that describe the blood-brain barrier is highly dependent on tissue T1-values measured prior to the administration of MRI contrast agents. This is, however, a time consuming step, and we compared different techniques with a pre-defined, literature based T1-value. The aim was to accommodate the balance between reliable data acquisition and the requirements on busy clinical departments. We found that the widely used Variable Flip Angle (VFA) technique is a considerable source of error in the calculation of quantitative parameters, whereas the Saturation Recovery technique, although as fast as the VFA method, is more reliable. If DCE is simply used as a qualitative method, however, our study showed that a pre-defined T1-value is sufficient. Pre-contrast T1-value measurements might therefore not be necessary in the daily clinical routine[4].

The prognosis of glioma patients is contingent on precise target selection for stereotactic biopsies and on the extent of tumor resection. 11C-methionine Positron Emission Tomography (PET) is thought to demonstrate tumor heterogeneity and invasion with high diagnostic accuracy. It is, however, an expensive and time-consuming procedure, and in contrast to MRI, only available at larger centers. In the third study, we compared the spatial distribution of a tumor, outlined by DSC and diffusion-weighted MRI, conventional MRI, and 11C-methionine PET. Assuming that 11C-methionine PET offers the best tumor delineation, we found that CBV maps are superior to conventional MRI in pre-operative imaging, particularly in HGGs, whereas tumor demarcation of LGGs remains a diagnostic challenge for both PET and MRI[5].

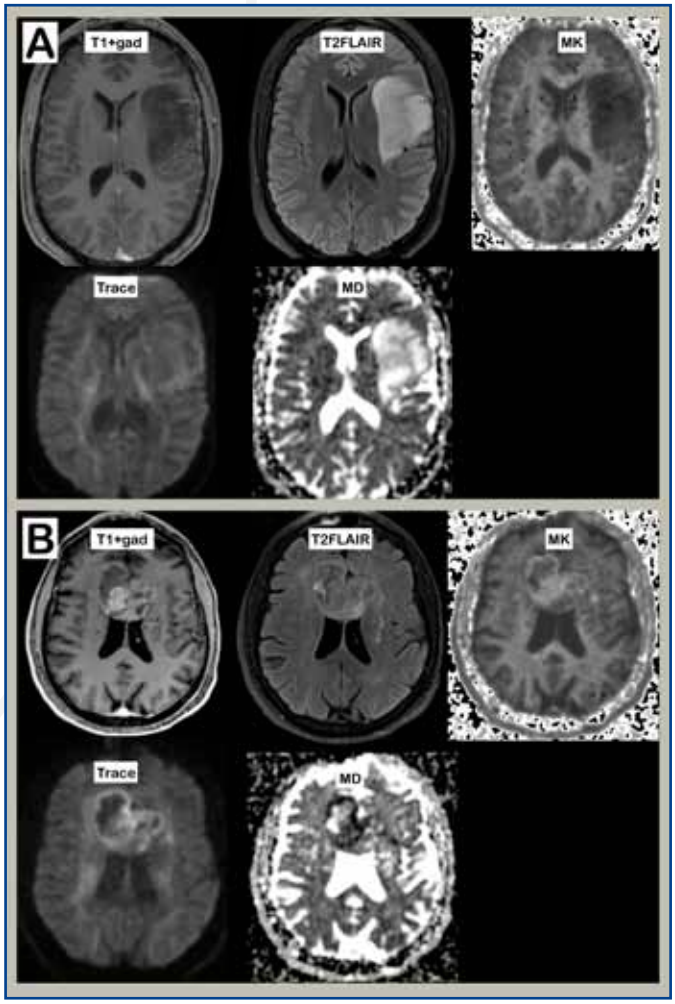

Figure 3
Mean Kurtosis (MK), acquired by the fast Diffusion Kurtosis Imaging (DKI) method is low in low grade gliomas (A) and high in high-grade gliomas (B). The DKI maps are compared to traditional diffusion-weighted MRI parameters (Trace and Apparent Diffusion Coefficient, ADC). Both techniques delineate different tumor regions.

In the fourth study, we investigated a relatively new MRI technique, Diffusion Kurtosis Imaging (DKI) that provides microstructural information on tissue. HGGs are characterized by a high cellular density due to extensive tumor cell mitoses. In addition, the development of micronecrosis, caused by hypoxia, is a diagnostic GBM criteria. DKI has been used to assess these changes in two prior studies, but its clinical implementation is hampered by very long acquisition times and complicated post-processing. A fast DKI scheme has recently been proposed[6], and we evaluated this method in 35 glioma patients with regard to tumor grading, only adding 3 min. of imaging and post-processing time (Figure 3). We compared our results to the literature and found that our method yields robust measurements. DKI, particularly in combination with traditional diffusion-weighted MRI, is a promising tool for grading and is likely to add valuable insights into tumor physiology, progression, and treatment monitoring[7].

In the last study, we implemented Magnetic Resonance Spectroscopy (MRS) into our routine pre-operative imaging protocol to detect Isocitrate Dehydrogenase (IDH) mutations in gliomas. The recent WHO upgrade of tumor classification requires a sub-classification into different genetic types, as mutations have an important prognostic implication and are

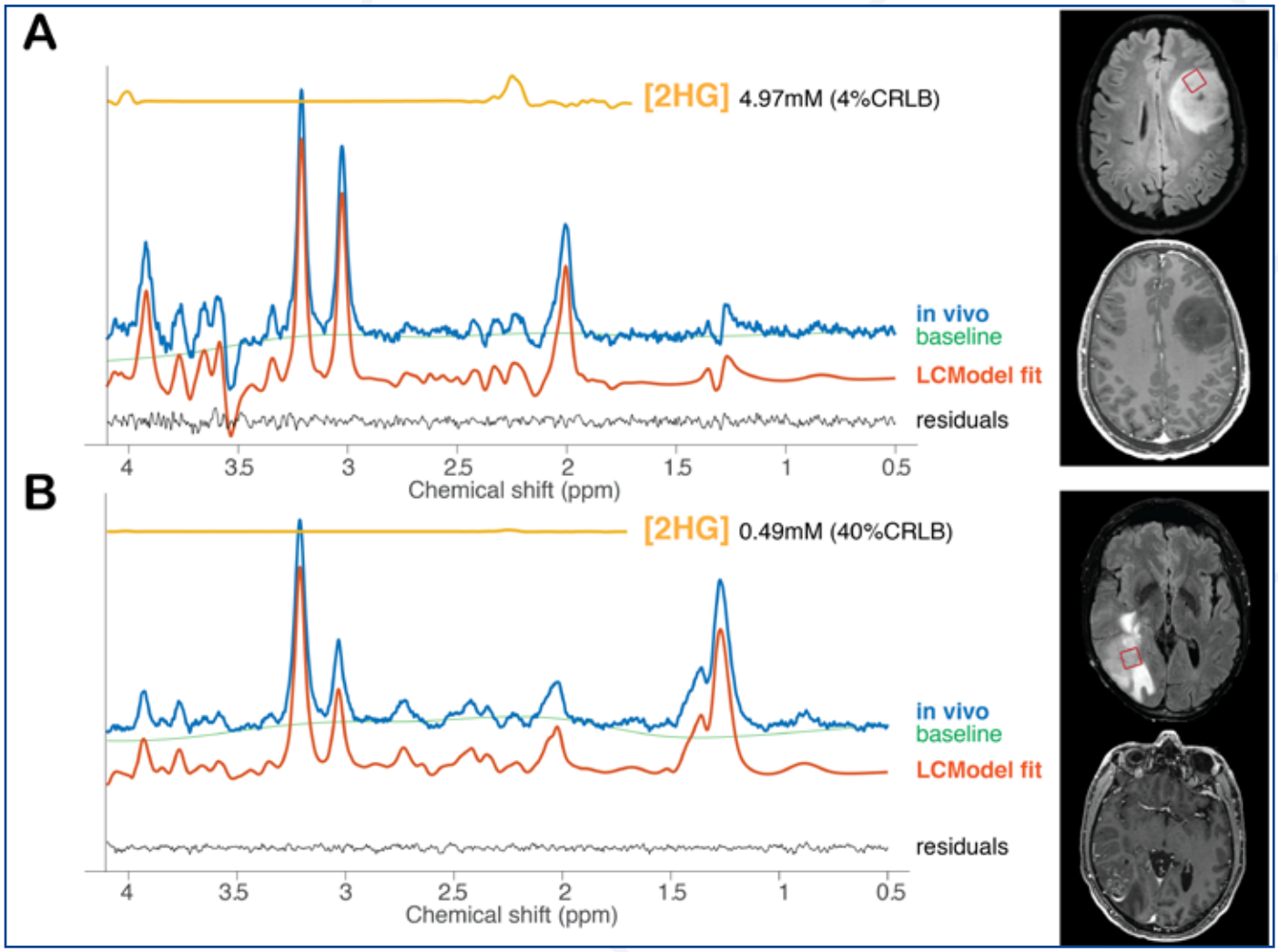

Figure 4
(A) MR Spectroscopy (MRS) results, T2FLAIR, and post-contrast T1-weighted images of an astrocytoma grade II. The MRS shows a peak at 2.25 p.p.m., where 2-hydroxyglutarate (2HG) protons are expected to resonate. 2HG is only produced in IDH mutated gliomas. Its concentration is estimated to be 4.97mM (± 4% CRLB). Polymerase chain reaction (PCR) verified a mutation in the IDH1 gene.
(B) For comparison, MRS, T2FLAIR, and post-contrast T1-weighted images of a wildetype glioblastoma is demonstrated. A sub-threshold 2HG concentration of 0.49mM (± 40%CRLB) is in agreement with a non-mutated glioma (proven by immunohistochemistry and PCR).

used for therapy stratification. IDH mutations are one of the most important molecular biomarkers and are usually verified in tissue biopsies. We compared our MRS results to findings obtained by immunohistochemistry and Polymerase Chain Reaction (PCR) in tissue biopsies and were able to detect IDH mutational status correctly with a sensitivity of 89.5% (specificity 81,3%) (Figure 4). The additional imaging time was under 5 min, allowing us to use this technique clinically in difficult diagnostic cases (differentiating gliomas from metastases and non-tumorous lesions) and for treatment monitoring.

This work has the potential to extend the diagnostic tools in both the pre-operative setting as well as during the follow-up period, when treatment failure and tumor progression have to be detected as early as possible. Reliable and detailed imaging is one important component to hopefully improve the outcome for glioma patients.

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Advanced Magnetic Resonance Imaging methods in cerebral glioma patients

On 23 September 2015 CFIN researcher and consultant at the Department of Neuroradiology, Aarhus University Hospital, **Anna Tietze** defended her PhD thesis.

Recent therapeutic advances in the treatment of patients with cerebral gliomas put great demands on Magnetic Resonance Imaging (MRI) strategies for therapy planning, outcome prediction, and treatment monitoring. The assessment of neo-angiogenesis, tumor hypoxia, or microstructural changes, such as cellularity and micronecrosis, has the potential to determine glioma subtypes. This allows more targeted and individualized treatment approaches, which eventually may result in improved patient outcome.

The objective of the PhD thesis entitled: “Advanced Magnetic Resonance Imaging methods in cerebral glioma patients” is to evaluate the role of advanced imaging biomarkers in glioma patients in terms of tumor grading and outcome prediction. A physiological model that describes microvascular changes in tumor angiogenesis in terms of capillary transit time heterogeneity is presented. Its implication for the oxygen extraction efficacy in tumor tissue is described, and the significance of this new imaging parameter as a diagnostic and predictive marker is evaluated.

FUNCTIONAL HEMODYNAMICS

Brain Microcirculation in Health and Disease

by Eugenio Gutiérrez Jiménez

Brain function depends on the adequate delivery of oxygen and nutrients through its blood supply. During functional activation, the blood supply increases in active brain regions. Neurovascular coupling denotes the mechanisms that adjust cerebral blood flow according to the local variations in metabolic needs (Roy & Sherrington, 1890).

Recently, the classical flow-diffusion model (Renkin, 1985) was extended to take capillary transit time heterogeneity (CTH) into account (Jespersen & Østergaard, 2012). The model shows that the homogenization of transit times counteracts the inherent reduction of oxygen extraction efficacy as flow increases. Indeed, subsequent analyses suggest that such homogenization is an intrinsic property of passive, compliant microvascular networks (Rasmussen, Jespersen, & Østergaard, 2015). However, the homogeneous distribution of capillary blood can be affected in different diseases. The failure to homogenize during an episode of hyperemia is known as capillary dysfunction (Østergaard et al., 2013).
In my thesis, I studied the effect of functional activation and vasodilators on the cerebral microcirculation in normal, aged and diseased brain. I estimated mean transit time (MTT) and CTH by two techniques using two-photon microscopy, as described in my first study (Gutiérrez Jiménez et al., 2016). The first method applied a modified version of a vascular transport method used in dynamic MRI. The second method calculated MTT and CTH using red blood cell velocities and fluxes measured in single capillaries.

In my first study, I analyzed the changes in plasma MTT and CTH during forepaw stimulation in anesthetized mice. I also analyzed the coefficient of variation (CoV = CTH/MTT), which was expected to remain constant in passive, compliant microvascular networks. The analysis showed that between arterioles and venules, functional activation produces a reduction of 11% in MTT, 30% in CTH, and 21% in CoV – see Figure 1. The reduction in CoV suggests that the homogenization of capillary transit times is larger than one would expect secondary to a passive increase in cerebral blood flow. This is consistent with a neurocapillary coupling mechanism, acting at the level of individual capillaries to facilitate oxygen extraction.

In my second study, I induced a passive dilation of the cortical microvasculature by hypercapnia in anesthetized mice. Moderate to severe hypercapnia produced a reduction in MTT and CTH as determined by the indicator-dilution method. The same effect was observed in the estimates derived from single capillary scans. CoV, however, increased during the massive hyperemia – see Figure 2. Some vascular units showed a relative increase in CTH compared to MTT, which might represent either or both capillary constriction and blood shunting through vascular thoroughfare channels.

In my third study I wanted to evaluate the effect of age and disease (Alzheimer's disease) on capillary transit times. I applied a similar paradigm as used in the first study to examine 18-months-old APPSwe/PS1ΔE9 transgenic mice (Tg) and their aged littermates (WT). The analysis of this study showed that the Tg mice displayed a state of hypoperfusion during the resting state, as compared with their littermates – see Figure

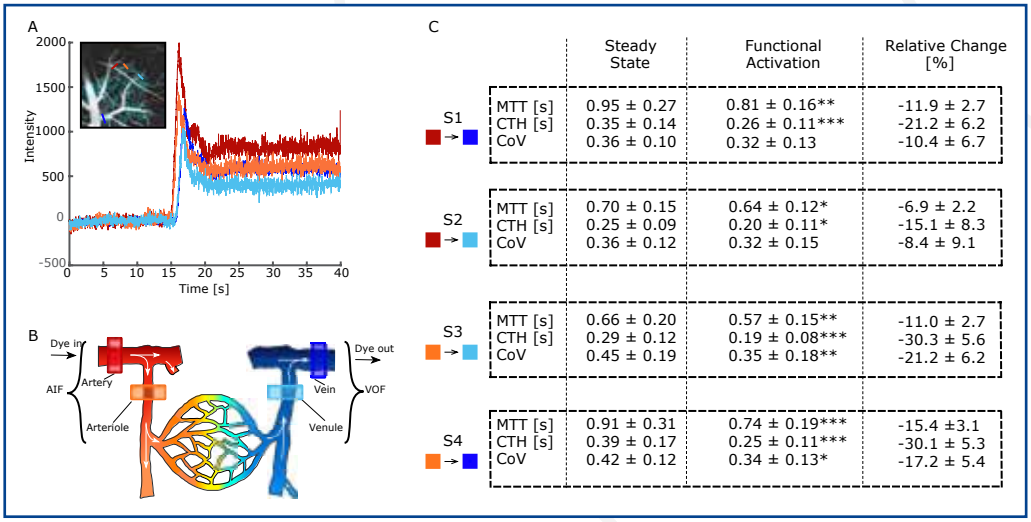

Figure 1
(A) Time courses obtained after bolus injection of dye from each vessel indicated in the reference image of Line-Scans (black square) show the differences in TTP between different blood vessels. Vessels were segmented according to their diameter and the TTP of their CTC. (B) Schematic drawing of the microcirculation, displaying the networks evaluated by this bolus tracking. The AIF was selected among the brain's feeding arteries, as the vessel with largest diameter and the first to enhance (dark red), whereas the venous output function (blue) was identified as the largest vein, last to enhance within the venous group. Also the anatomically related arteriole (orange) and venule (light blue), were identified and selected. (C) Estimations made of MTT, CTH, and CoV from dye bolus passage. Segments were assembled by pairs of the vessels selected (S1–S4). *p = 0.05, **p = 0.001, ***p < 0.001.
TTP: time-to-peak; CTC: concentration-time-curve; AIF: arterial input function; MTT: mean transit time; CTH: capillary transit-time heterogeneity; CoV: coefficient of variance.

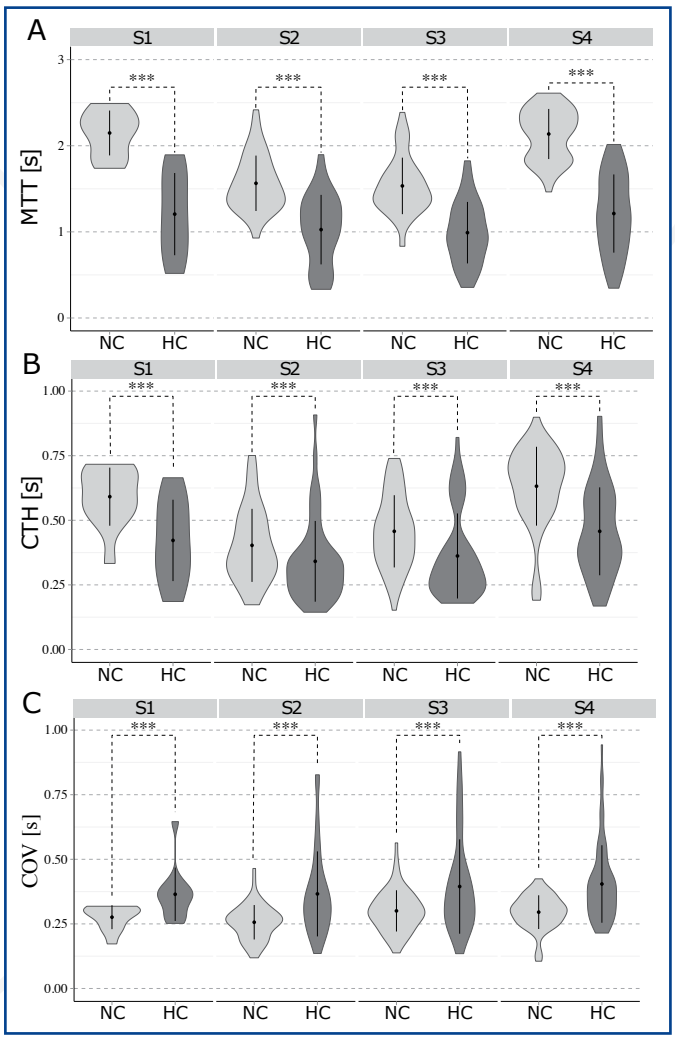

Figure 2
Violin plot of MTT (A), CTH (B) and CoV (C) estimates from bolus tracking measurements through all the vascular segments during normocapnia (NC) and hypercapnia (HC). (S1: artery – vein; S2: artery - venule; S3: arteriole – venules; S4: arteriole –vein). *p < 0.05, **p < 0.01, ***p < 0.001, error bars = S.D.

3. During functional activation, however, the Tg showed an augmented stimulus-response, seemingly compensating for the baseline hypoperfusion. Reductions in MTT and CTH in the transgenic mice were limited, while CoV was close to zero. The changes observed in the transgenic mice were much smaller than those observed in young healthy mice (in my first study) and seem to be consistent with a passive response to the low blood flow increase during steady state. Unexpectedly, the aged littermates showed a vasoconstriction of the pial vasculature during activation and a delay in the stimulus-evoked response in the capillary hemodynamics. In these aged control animals, we also observed an increase in CTH and CoV during functional activation, which suggest that the resulting change in capillary hemodynamics might introduce functional shunting, such that the hyperemic response fails to

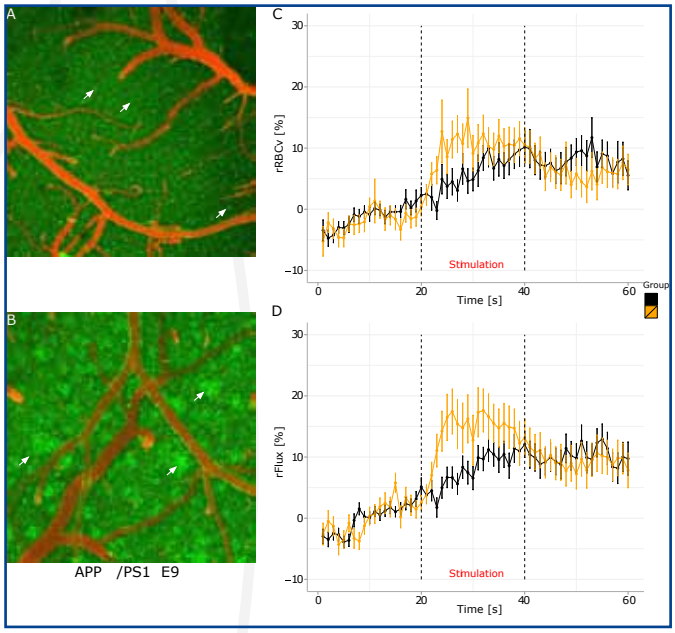

Figure 3
(A, B) Maximum intensity projection of the brain cortex and vasculature of aged mice (A, Control) and Alzheimer's disease mouse model (B, Tg). C and D show the average relative change (prefix 'r') of RBCv and RBC flux ± S.E.M. time-series. The Tg mice displayed a state of hypoperfusion during resting state, as compared with their WT littermates. During functional activation, however, the Tg showed an augmented perfusion-response, seemingly compensating for the baseline hypoperfusion. *p<0.05, **p<0.01, *** p<0.001. Error bars= S.E.M.

improve tissue oxygenation. As a consequence, aging seems to be parallelled by growing tissue hypoxia in these animal models.

Overall, the findings of my three studies support that capillary flow patterns play an important role in the optimal oxygenation of brain tissue in health and disease.

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TPML

Two-Photon Microscopy Laboratory

by Nina Kerting Iversen

The Two-Photon Microscopy Laboratory (TPML) at CFIN engages in interdisciplinary preclinical research with the overall goal to understand and quantify capillary dysfunction in various age-related disorders including ischemic stroke and reperfusion injuries, Alzheimer's disease, and diabetic neuropathy. The growing population of elderly in the western world puts a fundamental medical and economic premium on understanding the pathophysiology of these diseases to develop strategies to prevent and treat the growing number of such chronic, disabling condition. The CFIN TPML makes up one of the pillars of the interdisciplinary scientific Preclinical Research Facility (PiFa) at Aarhus University/ Aarhus University Hospital. By joining forces with the CFIN Preclinical MR-group, the PET research group and the CENSE group at the Neurosurgery Department of Aarhus University Hospital, we have the opportunity to employ an array of cutting edge scanning methods that in concert allow us to shed new light on brain disease mechanisms and hopefully inform development of future treatments.

NEW FACE at CFIN

Tristan Hollyer, BSc (Hons) Biomedical Science (Pharmacology), University of Aberdeen.

Tristan joined CFIN in June this year after completing his PhD thesis at the University of Glasgow where he investigated the use a stem cell therapy for pre-clinical stroke using functional imaging.

He is implementing his experience in in vivo physiology and pharmacology to investigate the role of lactate in the cerebral microcirculation homogenisation using microdialysis and two-photon microscopy.

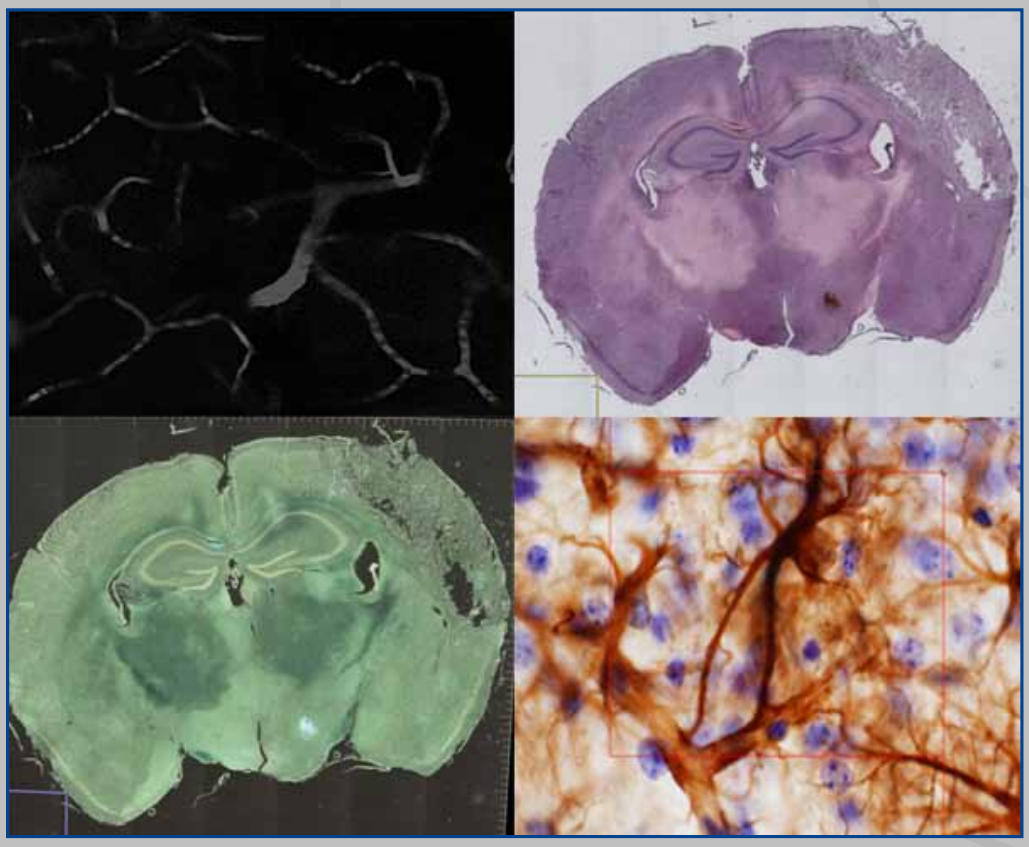


Figure 1
The effects of subarachnoid hemorrhage (SAH) on the flux of red blood cells in individual capillaries using a combination of Two-Photon Microscopy (a), for flux measurements of individual erythrocytes in cerebral capillaries in the damaged area, histological methods (b,c) for visualization and quantification of the damaged area, as well as stereological methods (bcd), making it possible to visualize individual neurons and demonstrate that these are highly damaged, by interrupting normal neurovascular coupling mechanisms.
Data from PhD student Maryam Anzabi and Post doc Maryam Ardalan.

Two-Photon microscopy

In 2012, the preclinical TPML was founded at CFIN through the installation of the Prarie Two-Photon Microscope. The microscope was funded by MIND*Lab* and provides us with the unique possibility to visualize and measure the flow of individual red blood cells in brain capillaries *in vivo* 3D in healthy and manipulated murine models as outlined in some of the research highlights below.

In collaboration with CFIN/MINDLab and ARCARDIA staff, post doc Eugenio Gutiérrez Jiménez has implemented and further developed a two-photon microscopy bolus tracking method to quantify capillary transit time heterogeneity (CTH) in murine cerebral capillary beds. He has used this method to demonstrate capillary dysfunction in murine models of Alzheimers Disease as well as to quantify how CTH is affected by the coupling of neuronal activity and blood supply, i.e. the neurovascular coupling mechanism. Read more of Eugenio's work at page 16-17. Such recent efforts and many others at TPML are uniquely enabled by postdoc Peter Mondrup Rasmussen and Irene Klærke Mikkelsen who have developed highly sophisticated software to analyze the large and complex data sets generated by the two-photon microscope. PhD student Maryam Anzabi has shed new light on the effects of subarachnoidal hemorrhage on the flux of red blood cells in individual capillaries using a multipronged approach that combines TPM, MR scanning techniques in collaboration with Associate Professor Brian Hansen and Assistant Professor Birgitte Kjølby, CFIN, and stereological methods in collaboration with postdoc Maryam Ardalan, Stereological Research Laboratory, Aarhus University Hospital. This experimental work has demonstrated the deleterious effect of bleeding in the brain and further shed light on the second phase of brain injury characterized by reduced level of consciousness and/or focal neurologic deficits, the so-called delayed cerebral ischemia. Figure 1 shows two-photon scannings of individual capillaries in a murine model of subarachnoidal hemorrhage and sterological investigation of the same brain demonstrating the deleterious effects of the bleeding. In early 2016, Maryam Anzabi got the possibility to undertake a 1-year research sojourn to Professor Chenk Ayata's laboratory at Athinoula A. Martinos Center for Biomedical Imaging at Harvard Medical School and Massachusetts General Hospital (MGH) to further her studies on the effects of subarachnoidal bleedings on spreading depolarisations and cerebral capillary blood flow.

FACTS

Core and affiliated groups members:

- Nina Kerting Iversen
- Eugenio Gutierrez Jimenez
- Maryam Anzabi
- Maryam Ardalan
- Anete Dudele
- Vibeke Bay Sørensen
- Tristan Hollyer
- Jesper Just
- Kim Ryun Drasbek
- Leif Østergaard
- Sebastian Frische
- Morten Skovgaard
- Luca Bordoni
- Jacob Engbjerg
- Niels Secher
- Frederik Hansen
- Susanne Schmidt Christensen
- Stine Ledet Methmann
- Peter Mondrup Rasmussen
- Irene Klærke Mikkelsen
- Rasmus Aamand

Conferences and International Research Visits:

- Eugenio Gutiérrez Jiménez Harvard Optics Division at the Athinoula A. Martinos Center for Biomedical Imaging at Harvard Medical School and Massachusetts General Hospital (MGH)
- Nina K. Iversen, Susanne Schmidt Christensen and Vibeke Bay Sørensen, Wellcome Surgical Institute, Institute of Neuroscience and Psychology College of Medical, Veterinary and Life Sciences University of Glasgow, UK
- Maryam Anzabi Optics Division at the Athinoula A. Martinos Center for Biomedical Imaging at Harvard Medical School and Massachusetts General Hospital (MGH)
- Eugenio Gutierrez Jimenez, Vibeke Bay Sørensen, Brain & PET 2015, 27th Symposium on Cerebral Blood Flow, Metabolism and Function, Vancouver, CA
- Anete Dudele Feldman Lab, Ann Arbor, University of Michigan, USA
- Kim Ryun Drasbek, Jesper Just, Society of Neuroscience, San Diego, November 2016.
- Leif Østergaard, Eugenio Gutierrez Jimenez, Peter Mondrup Rasmussen, Optics Division at the Athinoula A. Martinos Center for Biomedical Imaging at Harvard Medical School and Massachusetts General Hospital (MGH)
- Kim Ryun Drasbek, 9th International Symposium on Neuroprotection and Neurorepair, Leipzig, Germany.
- Jesper Just, Department of Nutritional Toxicology, Friedrich-Schiller-Universität Jena. Research group of Professor Dr. Tilman Grune.
- Jesper Just, Deutsche Institut für Ernährungsforschung, Potsdam – Rehbrücke. Research group of Professor Dr. Tilman Grune.

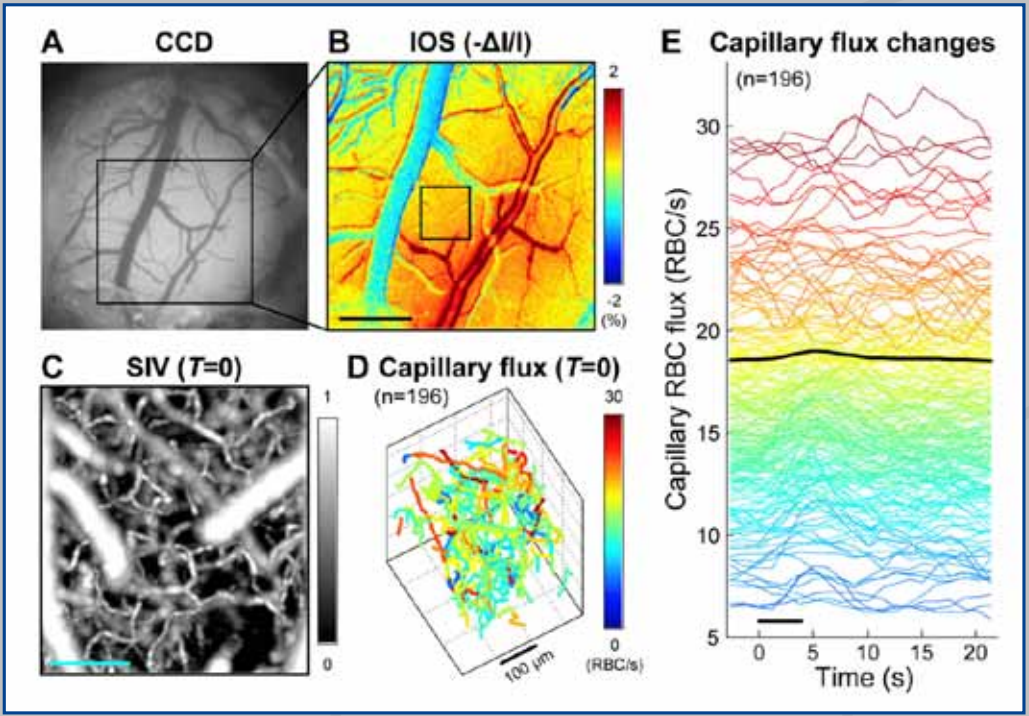


Figure 2
The Optical Coherence Tomography (OCT) system recently installed at CFIN in close collaboration with Professor David Boas's group at the Athinoula A. Martinos Center for Biomedical Imaging at Harvard Medical School and Massachusetts General Hospital (MGH) enables us to study the flux of each individual erythrocyte in up to 500 capillaries at a time. This will allow us to demonstrate how micro vascular diseases affects the capillary transit time heterogeneity (CTH), and thereby the oxygenation of the tissue, in various age-related disorders. Figure adapted from Lee et al., 2014. Statistical intensity variation analysis for rapid volumetric imaging of capillary network flux. Biomedical Optics Express 5, 4 1160-1172.

NEW FACE at CFIN

Anete Dudele, MSc, PhD. Anete joined CFIN in February 2016 as a post-doctoral researcher.

She holds a PhD degree in Bioscience awarded by the Faculty of Science and Technology, Aarhus University. During her PhD she worked with rodent models of diabetes and inflammation, primarily focusing on why and how maternal obesity during pregnancy causes offspring obesity and diabetes.

Her post-doctoral research project is a part of the International Diabetic Neuropathy Consortium (IDNC) during which she will investigate the role of capillary (dys-) function in development of diabetic neuropathy in mouse models. She will study this using two photon microscopy and OCT.

NEW FACE at CFIN

Jesper Just, MSc, PhD, Postdoc at CFIN since May 2016 in the group of Kim Ryun Drasbek.

Jesper received his PhD in the field of Recombinant Antibody Technology from Department of Molecular Biology & Genetics, Aarhus University. During his PhD, Jesper used recombinant antibodies as explorative tools to discover novel biomarkers and went on research stays at Department of Nutritional Toxicology, Friedrich-Schiller-Universität Jena and Deutsche Institut für Ernährungsforschung.

Jesper is working on the project entitled "Conditioning-based intervention strategies – ConBIS" funded by the Novo Nordisk Foundation, where he applies experimental and bioinformatics tools to profile stroke protective micro-RNAs induced by Remote Ischemic Conditioning.

Optical Coherence Tomography

The Two-Photon microscope permits us to image blood flow in 5-10 capillaries at a time, thus providing a highly detailed measure of CTH and individual capillaries in a limited part of the brain but with a very high resolution. To study the effect of compromised blood flows as parameterized by CTH on tissue oxygenation over a larger area in the brain, concomitant imaging of individual erythrocyte fluxes across a large brain volume and hence more capillaries are needed. Until recently, computational and technological challenges have prohibited such large-volume measurements. However, the Optical Coherence Tomography (OCT) technique may overcome these challenges by using coherence gating to collect light only scattered from moving erythrocytes in a large tissue volume for high-resolution structural imaging. Our close collaborators at Professor David Boas' laboratory at the Athinoula A. Martinos Center for Biomedical Imaging at Harvard Medical School and Massachusetts General Hospital (MGH) have just succeeded in developing OCT acquisition algorithms and analysis tools that permits them to measure capillary flow velocities across many capillaries (4-500) and large tissue volumes with high temporal resolution (see Figure 2). Via support from the VELUX foundation we have purchased an OCT system from Thorlab to be used in close collaboration with David Boas' group. In the fall of 2015, Associate Professor Jonghwan Lee visited CFIN to start the first part of the software installation and in early 2016, postdoc Baoqiang Li followed to elaborate on the new software developed to the system. The first *in vivo* data at CFIN were acquired during the summer 2016, and in September, Eugenio Gutiérrez Jiménez, Peter Mondrup Rasmussen and Leif Østergaard attended a meeting in Boston to further data analysis and software development of this highly promising technique.

FACTS

Selected on-going research projects:

- Nina K. Iversen: Acute cerebral ischemia and reperfusion injury: the role of capillary transit time heterogeneity.
- Eugenio Gutierrez Jimenez: Brain Microcirculation in health and disease.
- Vibeke Bay Sørensen: The X-factor: Identifying the blood borne factor that conveys ischemic protection following remote conditioning.
- Anete Dudele: The role of hypoxic nerve damage in development of Diabetic Neuropathy
- Luca Bordoni: The Role of AQP4 and Cerebral Capillary Blood Flow Dynamics in development of Hyponatremia induced Brain Edema in Mice
- Tristan Hollyer: The role of lactate in the cerebral microcirculation
- Jacob Engbjerg: Is the dynamics of glomerular capillary blood flow altered in diabetes?
- Jesper Just: Conditioning-based intervention strategies – ConBIS. An expanded potential of remote conditioning for activation of endogenous organ protection and rebuilding the underlying molecular mechanisms.
- Maryam Anzabi: Influence of pericapillary nitric oxide levels and edema on capillary blood flow patterns in rat models of subarachnoid hemorrhage
- Maryam Ardalan: The Influence of Rapid-acting Antidepressants on the Neuronal and Non-neuronal Plasticity of the Hippocampus in a Genetic Rat Model of Depression.

Neuroscience in China

by Kim Ryun Drasbek

The Master's programme in Neuroscience and Neuroimaging in Beijing, China is part of the Sino-Danish Center for Education and Research (SDC). CFIN researchers contributed greatly to the design and development of the education and remains deeply involved in the programme. It is a national initiative that also involves colleagues from the Danish neuroscience community to support the Master's programme and seek scientific collaboration with Chinese partners.

The Master's programme in Neuroscience and Neuroimaging is one of seven 2-year Master's educations in the SDC collaboration. Since the start in 2012 three classes of students have graduated obtaining degrees from both Aarhus University and University of Chinese Academy of Sciences. A number of them are pursuing a research career and are enrolled as PhD students in Europe, China, or Denmark. Some of the PhD students in Denmark and China are being funded by SDC and working on collaborative projects between labs from the two countries. In relation to CFIN, two Danish PhD students are doing part of their studies in China, while two Chinese SDC funded PhDs will visit CFIN during 2017 for half a year to obtain double degrees.

All the Chinese Master's students come to Denmark for a 2-month visit in the spring of their second year. They stay at their Danish co-supervisors lab. For most of them, it is their first trip outside of China and it is a good experience for them to get to know the work environment in a Danish lab. While they are here, they travel a bit around Denmark and some also plan to visit several European countries during Danish holidays.

We arrange annual symposia for the Neuroscience and Neuroimaging Master's programme, during which all 2nd year students presents their research project. For some of the students this presentation represents the official Opening Speech for their Chinese Master's degree. At the symposium, the 2nd year Master's students get valuable feedback for their project from fellow students, supervisors, and Chinese and Danish neuroscientists. The symposium is usually coupled to scientific sessions which give the attending scientists an opportunity to present their work and discuss future collaborations. Also, more detailed project meetings are now taking place between project supervisors, students, and other collaborators during these meetings where a number of the SDC involved neuroscientist have an opportunity to meet and interact.

In early 2015, a program coordinator, Vibeke Sauer Panyella was employed to help the Head of Educational Programme run the education in China. The students have clearly appreciated the help she has provided. She continues to work towards better work flows, plans, etc. to help both the students and the teaching teams of the different courses. She is also deeply involved in the recruitment of students for the education as well as the continued development of the education.

Chinese students visit CFIN
During their visit to Denmark, all second year students visited CFIN in Aarhus where the students were on tour through the imaging and lab facilities and were introduced to some of the techniques used at CFIN: MEG/EEG by MEG Engineer Christopher Bailey, PET scanning by Associate Professor Arne Møller, and MR scanning by Research Radiographer Dora Zeidler.

Photo: Vibeke Sauer Panyella

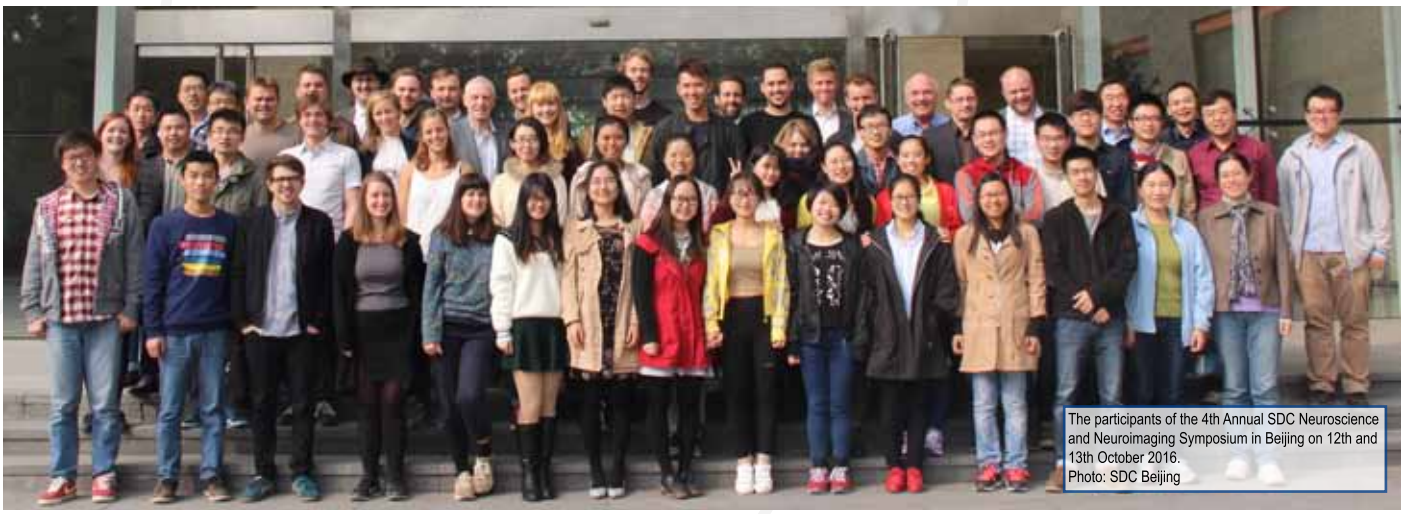
List of CFIN / MIND*Lab* researchers involved in SDC teaching and coordination

Andrey Chuhutin
Arne Møller
Birgitte Fuglsang Kjølby
Carsten Gleesborg
Chris Bailey
Dora Zeidler
Jens Kjærgaard Boldsen
Kim Mouridsen
Kim Ryun Drasbek
Peter Mondrup Rasmussen
Simon Eskildsen
Sune Jespersen
Thomas Alrik Sørensen
Vibeke Sauer Panyella
Visse Moestrup

NEW FACE at CFIN

Vibeke Sauer Panyella, MSc. Vibeke has a Master's degree in Biology from Aarhus University, she wrote her thesis at Centre for Science Education. During her studies, she worked as a student counsellor, and was a member of the Board of Studies for a number of years.

In February 2015 Vibeke was hired as program coordinator for SDC Neuroscience & Neuroimaging. Her main job is to make sure that the Master's programme runs as smoothly and structured as possible. Vibeke has become a part of the CFIN administration and as such helps with some of the tasks that arises there.



The participants of the 4th Annual SDC Neuroscience and Neuroimaging Symposium in Beijing on 12th and 13th October 2016.
Photo: SDC Beijing

Chinese students visit CFIN

During their visit to Denmark, all students are assembled at CFIN for a general introduction to living and studying in Denmark. The students are invited to give a short talk about their experiences during their stay and what they have achieved in the lab of their Danish supervisor. They also participate in writing sessions in relation to their master thesis.

Photo: Kim Ryun Drasbek

APPLIED IMAGING AND MODELLING

by Simon Fristed Eskildsen

Applied Imaging and Modelling

The applied imaging and modelling (AIM) group investigates pathological and developmental changes in the brain using various imaging modalities and analyses methods. One of the major focus areas is Alzheimer's disease (AD), and during 2015 and 2016 our group delved deeper into the microvascular hemodynamic properties of the Alzheimer brain. CFIN researchers have previously shown that the distribution of blood flow through the capillaries affects oxygen delivery to the tissue and that optimal oxygen extraction exists when capillary flows are homogenous (Jespersen and Østergaard, 2012). In AD, capillaries are altered by morphological changes in the vessel walls, and it is hypothesized that these alterations disturb the capillary blood flow and limit oxygen extraction, leading to hypoxia, which is known to facilitate the deposition of neurotoxic proteins in brain tissue and ultimately causes cognitive decline (Østergaard et al., 2013). By applying dynamic susceptibility contrast (DSC) MRI and parametric modelling (Mouridsen et al., 2014), the AIM group was able to detect this hypothesized phenomenon in two independent cohorts.

In a clinical cohort consisting of AD patients and patients with mild cognitive impairment (MCI) we found increased capillary transit time heterogeneity compared to age-matched controls in neocortex. Our model of oxygen delivery showed disturbed oxygen extraction capacity caused by the observed hemodynamic changes in the microvasculature. In addition, our measurements of capillary dysfunction correlated with cognitive symptoms and amount of white matter hyperintensities – a measure of small vessel disease (Figure 1). Our findings were published in Neurobiology of Aging (Eskildsen et al., 2016). In a second cohort consisting of 23 AD patients scanned twice at 6 months interval, we found that longitudinal changes in our marker of capillary dysfunction, the relative capillary transit time heterogeneity (RTH), correlated with changes in cognitive function (Figure 2A). Modelling the tissue oxygen tension, which may indicate current or imminent tissue hypoxia, we found widespread correlation with cognitive decline throughout neocortex at baseline (Figure 2B). These results will appear in Alzheimer & Dementia in 2017.

Together, these findings are encouraging and hold promises for the ongoing project on investigating perfusion changes in prodromal AD, also known as MCI. In collaboration with Professor David Brooks, the patients' brains are scrutinized by applying positron emission tomography (PET) to determine accumulation of neurotoxic proteins (amyloid β and Tau) and neuroinflammation and by applying MRI to determine degree of capillary dysfunction, tissue microstructural integrity, and degeneration. Baseline data for this ambitious

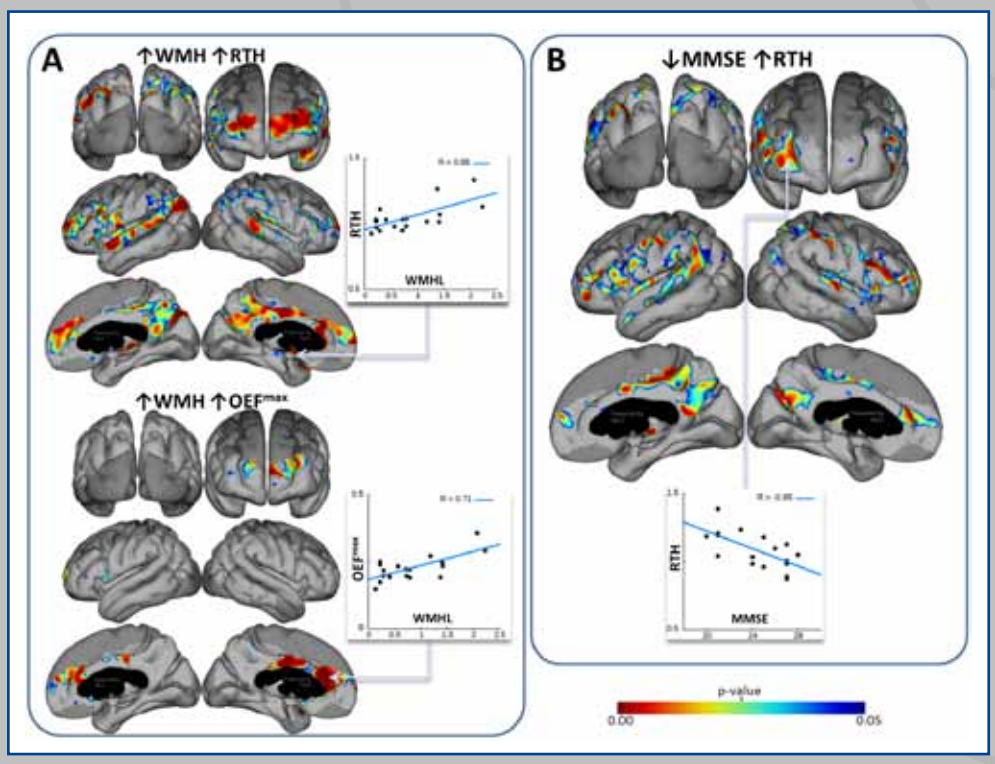


Figure 1
Panel A: statistical maps showing significant ($p<0.05$) correlates of white matter hyperintensities (WMH) with relative capillary transit time heterogeneity (RTH, upper map) and maximum oxygen extraction fraction (OEFmax, lower map) in patients.
Panel B: statistical map showing significant ($p<0.05$) negative correlation between mini-mental state examination (MMSE) scores and RTH. Statistical maps corrected for cortical thickness, gender and age. Plots show mean values for clusters surviving family-wise error correction. Adapted from (Eskildsen et al., 2016).

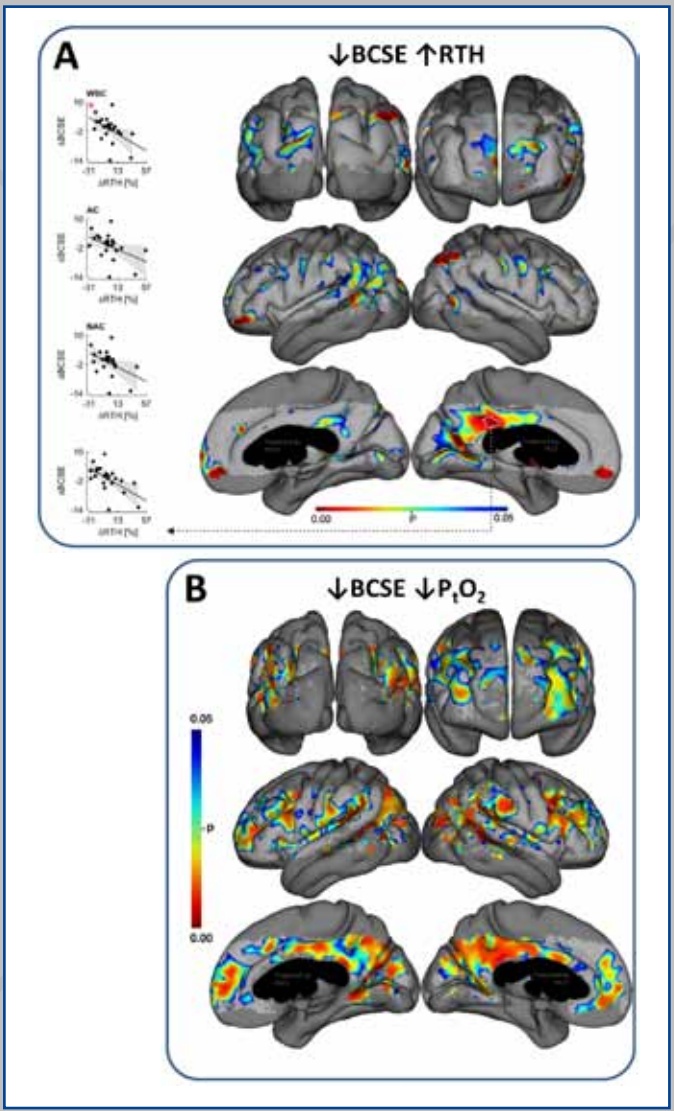


Figure 2
Panel A: six months change in Brief Cognitive Status Exam score (BCSE) correlated with six months change in relative transit time heterogeneity (RTH) across the cortical surface or mean regions of interest: whole brain cortical grey matter (WBC), atrophic cortical grey matter (AC), non-atrophic cortical grey matter (NAC) and a post hoc defined region (arrow).
Panel B: BCSE score correlated with derived tissue oxygen tension (PtO2) at baseline, using linear regression. Statistical maps are adjusted for age, thresholded at p<0.05, and adjusted for multiple comparisons using false discovery rate. Adapted from (Nielsen et al., 2016).

project was completed in 2016 and the two year follow-up will continue to the end of 2018. If our findings suggest that the microvasculature is compromised prior to accumulation of neurotoxic proteins in the brain, this will challenge the conventional theory of the AD etiology and suggest a new therapeutic target for the disease.

FACTS

Core and affiliated group members:

- Simon Fristed Eskildsen
- Rune Bæksager Nielsen
- Leif Østergaard
- Torben Ellegaard Lund
- Sune Nørhøj Jespersen
- Brian Hansen
- Kim Mouridsen
- Jesper Frandsen
- Irene Klærke Mikkelsen
- Mikkel Bo Hansen
- Lars Ribe
- Jakob Udby Blicher
- Erhard Trillingsgaard Næss-Schmidt
- Thorbjørn Engedahl
- Simon Hjerrild
- Anna Tietze

National & International collaborators:

- Professor David Brooks, Positron Emission Tomography Center, Department of Clinical Medicine, Aarhus University, Denmark.
- Professor Louis Collins, McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, Canada.
- Dr. Pierrick Coupé, Laboratoire Bordelais de Recherche en Informatique, Unité Mixte de Recherche CNRS (UMR 5800), Bordeaux, France.
- Professor José Manjon, Instituto de Aplicaciones de las Tecnologías de la Información y de las Comunicaciones Avanzadas (ITACA), Universitat Politècnica de València, Valencia, Spain.
- Dr. Rikke B. Dalby, Centre for Psychiatric Research, Aarhus University Hospital, Risskov, Denmark.
- Dr. Tim Dyrby, Diffusion Imaging Group, Danish Research Centre for Magnetic Resonance, Hvidovre, Denmark.
- Professor Marc Vérin, Institut des Neurosciences Cliniques de Rennes, Université Rennes, France.
- Professor Risto Kauppinen, School of Experimental Psychology, University of Bristol, United Kingdom.
- Professor Vibeke Hjortdal, Department of Thoracic and Cardiovascular Surgery, Aarhus University Hospital, Skejby, Denmark.
- Dr. William Baaré, Danish Research Centre for Magnetic Resonance, Hvidovre, Denmark.
- Dr. Eduardo A. Garza-Villarreal, National Institute of Psychiatry, Mexico

International research visits:

Yuri E. Rodrigues, Integrated Laboratory of Scientific Computing, Universidade Federal do Rio Grande do Sul, Brazil, visited the AIM group, February - June 2016.

Rune Nielsen visited PICTURA Research Group, Laboratoire Bordelais de Recherche en Informatique, Université de Bordeaux, June - July 2016.

Invited oral presentations:

Simon Eskildsen: Delegation from University of Queensland, Rector's Office, June 2015.

Simon Eskildsen: Laboratoire Bordelais de Recherche en Informatique, Université de Bordeaux, June 2016.

Simon Eskildsen: Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, October 2016.

The significance of an accurate segmentation

In neuroimaging, the disease effects we are looking for are often subtle and transient. We continuously push the limits for what we can detect in the living brain using ever more sophisticated machinery, optics, chemical tracers and data processing. Often the effects we are looking for are confined to specific brain regions, be that of anatomical or functional definition. We rely on automatic processing tools to provide us with these regions, and usually without questioning their accuracy or the impact on our measurements. In a PhD study looking for very subtle changes in brain tissue structure of individuals who suffered a concussion, Dr. Erhard Næss-Schmidt investigated the impact of using automatic processing tools for the analysis of tissue integrity metrics from MRI diffusion tensor imaging (Naess-Schmidt et al., 2016). He showed that group average segmentation volumes can vary up to 40% using conventional tools, such as SPM, FSL and Freesurfer (Figure 3). This variation resulted in differences of diffusion measurements of up to 10% on average compared to gold standard manual segmentation in healthy volunteers. Such variation may conceal important pathological phenomena and impair the sensitivity of imaging biomarkers. However, Dr. Næss-Schmidt also showed that the variation may be considerably lowered by applying more recent segmentation methods (Coupe et al., 2012) resulting in volumes and diffusion measurements similar to those obtained from manual segmentations. Applying these recent methods, he continued to measure tissue microstructural changes in the brain caused by concussion also known as mild traumatic brain injury (Næss-Schmidt et al., 2016). Dr. Næss-Schmidt defended his PhD thesis in November 2016.

Viruses and drugs

Our various interdisciplinary collaborations lead to many interesting studies and results. One of these studies examines neurobiological changes associated with chronic hepatitis C virus (HCV). HCV patients often suffer from fatigue, depression and cognitive impairment and the cause of these symptoms remain unknown. Affiliated PhD student Simon Hjerrild collected 43 HCV patients and 43 matched controls, one of the largest cohorts of its kind. We showed, among other things, that chronic hepatitis C virus infection leads to reduced cortical thickness (Hjerrild et al., 2016). Dr. Hjerrild defended his PhD thesis in June 2015 titled ”Neuropsychiatric aspects of chronic hepatitis C virus infection”.

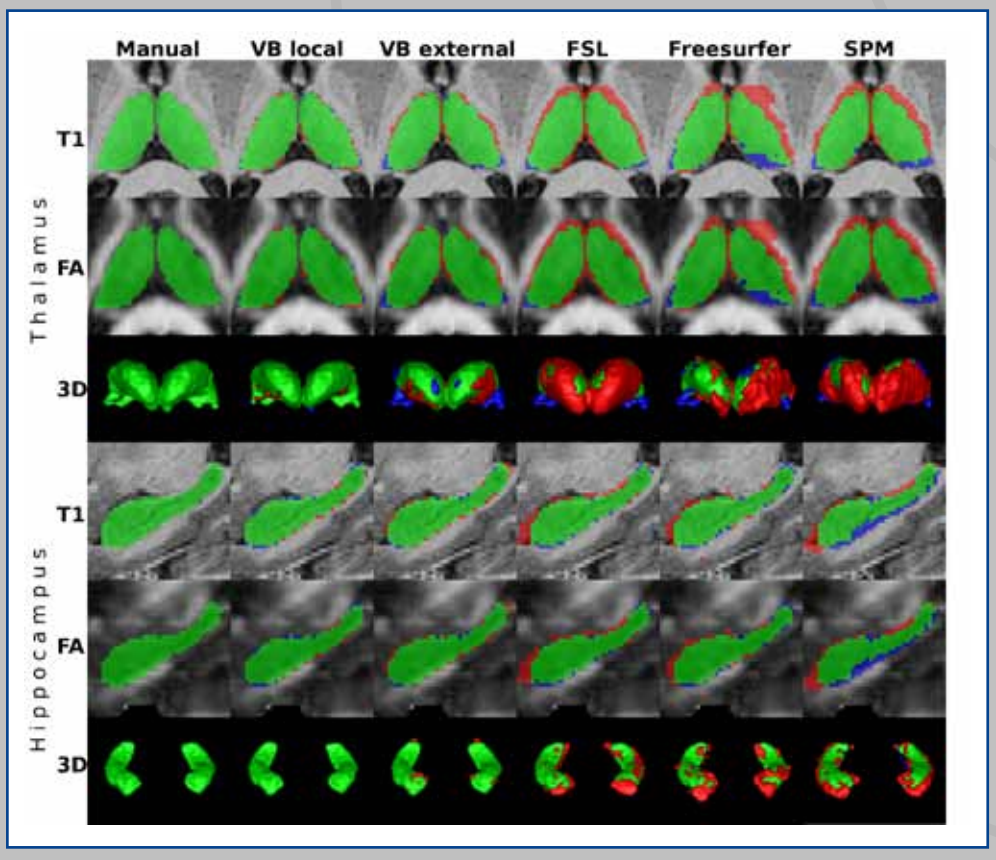


Figure 3
Examples of manual and automatic segmentations of thalamus and hippocampus. Upper two rows: thalamus in an axial view, overlaid on native T1-weighted and co-registered FA images. Third row: 3D reconstructions of thalamus. The lower three rows contain similar visualizations for hippocampus segmentations. Left to right columns: manual, volBrain local, volBrain external, FSL, FreeSurfer and SPM methods. Green areas indicate overlap between automatic methods and manual segmentation. Red indicates areas, which are included in the automatic, but not the manual method (false positives). Blue indicates areas, which are included by the manual, but not the automatic method (false negatives). Adapted from (Næss-Schmidt et al., 2016).

In collaboration with Dr. Eduardo A. Garza-Villarreal from the National Institute of Psychiatry, Mexico, we investigated subcortical changes in cocaine addiction. Using structural MRI we found significant contraction of nucleus accumbens in cocaine addicts compared to healthy controls (Garza-Villarreal et al., 2016). Applying the fast diffusional kurtosis imaging developed at CFIN (Hansen et al., 2013), we demonstrated significant age related changes in mean kurtosis of cocaine addicts in striatum and thalamus that are opposite to those seen in normal brain aging. This decrease in mean kurtosis may reflect loss of neurites, leading to fewer cell connections, decreased tissue integrity and increased extra-cellular space associated with cocaine addiction.

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FACTS

Conferences and meetings:

- AAIC 2015 – Simon Eskildsen (oral presentation)
- MICCAI 2015 – Erhard Næss-Schmidt (poster) and Simon Eskildsen
- FENS 2016 – Rune Nielsen (poster) and Simon Eskildsen (poster)
- PhD day 2015, Rune Nielsen (poster) and Simon Eskildsen (chairman)
- Neuroscience day, April 2015, Rune Nielsen (poster) and Simon Eskildsen
- Aarhus CTH meeting 2015 – Simon Eskildsen
- PhD day 2016, Rune Nielsen (poster) and Simon Eskildsen (chairman) - Rune Nielsen won the award for "Best poster presentation"
- DeKay meeting, April 2016 – Simon Eskildsen
- Neuroscience day, May 2016 – Rune Nielsen (poster) and Simon Eskildsen
- SDC symposium, October 2016 – Simon Eskildsen (chairman)
- Herrenhausen symposium, October 2016– Rune Nielsen
- Patch-MI workshop program committee, 2015, 2016 – Simon Eskildsen

Selected research projects:

Rune B. Nielsen, Simon F. Eskildsen, Leif Østergaard: Magnetic resonance imaging biomarkers in Alzheimer's disease: investigating capillary dysfunction and neurodegeneration for diagnosis and prediction.

Simon F. Eskildsen, Pierrick Coupé, Vladimir Fonov, Louis Collins: Prediction of Alzheimer's disease progression using structural MRI.

Rune B. Nielsen, Lærke Egefjord, Simon F. Eskildsen, Arne Møller, Hans Brændgaard, Jørgen Rungby, Leif Østergaard: Capillary flow changes in Alzheimer's disease.

Peter Parbo, Simon Eskildsen, Michael Winterdahl, Nicola Pavese, Leif Østergaard, David Brooks: The relationship between Aβ, inflammation and capillary dysfunction in amnestic mild cognitive impairment

Rikke B. Dalby, Simon F. Eskildsen, Poul Videbech, Leif Østergaard: Cerebral perfusion in patients with late-onset major depression.

Simon Hjerrild, Simon F. Eskildsen, Leif Østergaard, Poul Videbech: Cerebral cortical thickness and perfusion in non-cirrhotic patients with hepatitis C.

Simon F. Eskildsen, Henrik Lundell, Tim Dyrby: Cortical thickness and structural connectivity in the Vervet monkey brain.

Florence Le Jeune, Simon Eskildsen, Gabriel Robert, Claire Haegelen, Louis Collins, Marc Vérin: Structural and metabolic correlates of apathy induced by subthalamic stimulation.

Tormod Fladby, Ole Andreassen, Dag Årsland, Clive Ballard, Leif Østergaard, Lars Nilsson, Atle Bjørnerud: Pre-clinical genotype-phenotype predictors of Alzheimer's disease and other dementia.

Per Qvist, Steffen Ringgaard, Simon F. Eskildsen, Anders Børglum: The implication of the schizophrenia-associated gene, BRD1, in behavior, cognition and brain development in genetically modified mice.

Eduardo A Garza-Villarreal, Mallar Chakravarty, Brian Hansen, Sune Jespersen, Simon Eskildsen: Brain morphology and connectivity in cocaine addiction.

Erhard Næss-Schmidt, Jakob Blicher, Simon Eskildsen, Anna Tietze, Brian Hansen, Peter Stubbs, Mikkel Petersen, Sune Jespersen, Leif Østergaard, Jørgen Feldbæk Nielsen: Microstructural changes in the middle brain and post-concussion symptoms after mild traumatic brain injury - a diffusion MRI study.

Simon Eskildsen, Terry Jernigan, Wesley Thompsen, Kathrine Skak Madsen, William Baaré: Mapping of cortical maturational trajectories in children and adolescents.

NEUROINFORMATICS

2015 & 2016

by Kim Mouridsen

In 2015-2016 we have seen exciting new scientific results, entered into many new collaborations and gained commercial interest for our AU spin-out company Combat Stroke.

The group has continued its development and applications of the clinical MRI and CT-based markers of capillary integrity and perfusion. Our recent work, presented below, extends the areas of application from brain only (with T2* measurements) to the whole body by accommodating dynamic T1 measurements. The MRI software was recently central in a study lead by Dr. Patricia Musolino and Dr. Arne Lauer at Massachusetts General Hospital in the pediatric disease Adrenoleukodystrophy (or Lorenzo's Oil Disease). Despite a fatal prognosis, no biomarkers have been able to predict which at-risk patients will progress to the aggressive type of the disease. Dr. Arne Lauer was awarded the MGH Award for Best Neurology Research in 2015 for demonstrating that the biomarkers developed at CFIN and MIND*Lab* predicted disease onset up to 6 months before other imaging modalities, potentially allowing timely, but complex, treatment to be initiated.

Meanwhile Dr. Anna Tietze successfully defended her PhD thesis demonstrating that the capillary transit time heterogeneity (CTH) marker significantly improves tumor grading and prediction of adverse events. We have also been fortunate to enter collaborations with Charité University Hospital in Berlin, The University Hospital Heidelberg and the German Cancer Research Center, which have already lead to a series of publications. Most recently our group sparked a formal collaboration between Aarhus University and Harvard Medical School/Massachusetts General Hospital, which will see co-financing of research in microcirculatory imaging.

In parallel, we are increasing our activities in decision support technologies based on large data collections and computer intensive methods. Michelle Livne has demonstrated that whereas traditional decision trees are convenient for 'manual' decision making, building large sets of relatively small trees achieves state-of-the-art performance in predicting tissue outcome in acute stroke. At the same time, Anne Nielsen is demonstrating the potential in a special type of deep learning, called convolutional neural networks, in automatically extracting subtle features in acute MRI images to accurately predict stroke outcome (read more about this project on page 32-33). We are furthering our efforts in extracting actionable information from complex medical data through a new collaboration with the Hospital Clinic for Innovative Patient Pathways in Silkeborg, under Aarhus University, where we are analyzing diverse longitudinal data in patients with diffuse symptoms but suspected to have a serious disease, so as to potentially guide and accelerate the diagnostic workup.

Aarhus University co-founded the spin-out company Combat Stroke in 2013, and after initial market activities the company secured a substantial second round of investment in 2015 lead by London-based Smedvig Capital. CEO of the Smedvig Family Office, Odd Torland, is now the Head of Board of Directors while CSO Marit Salte joins as a member of the BoD. Combat Stroke further secured Horizon 2020 funding from the Innovation Associate program, which focuses on attracting international expertise to accelerate market readiness.

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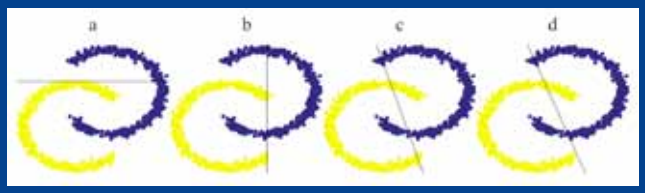
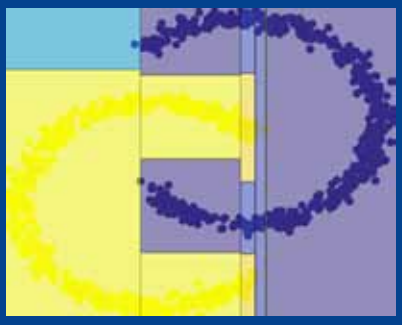
ATLAS: Automatic Tree Learning Anomaly Segmentation



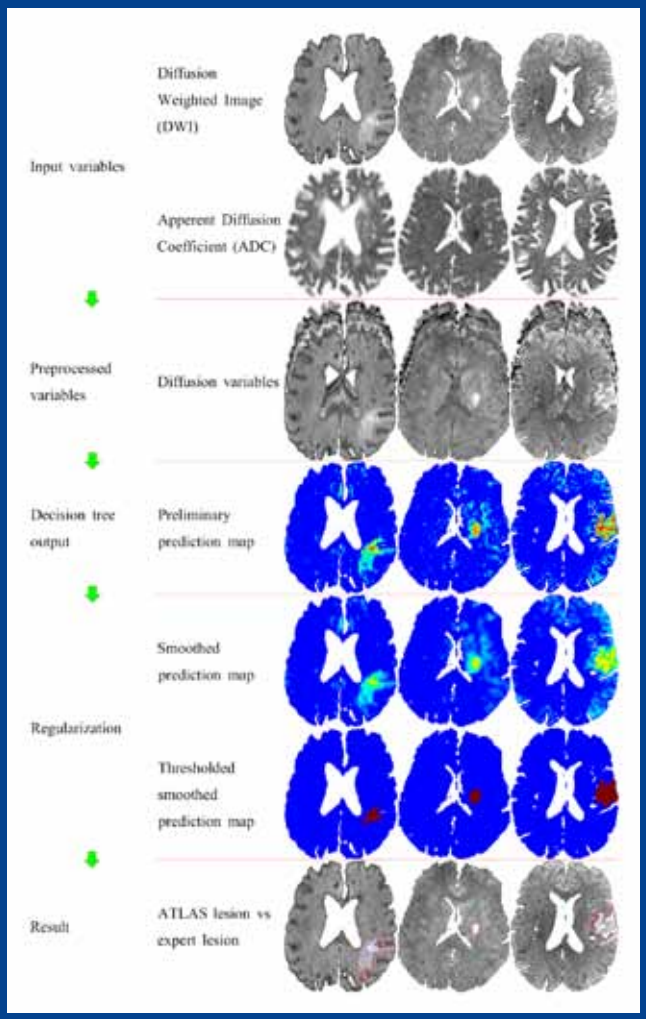
Identifying the acute core lesion is critical in triaging stroke patients. Many methods have been proposed for segmenting the core lesion. Most automatic segmentation methods use one or two fixed or relatively fixed thresholds on a diffusion scan to accomplish this. However, if we want precise results these methods are inadequate in all but the simplest of situations. In the example below you see a point set divided into two classes by some of the most common methods (a, b: best one variable threshold, c: logistic regression, d: Fisher's discriminant), while some of them clearly are better than others, none of them seem to capture the shape of the two classes.

A decision tree is a method of dividing data into boxes by recursive thresholding - i.e. you start by dividing the data into two boxes using the best possible threshold (for some value of best possible), and you repeat this process for each of the two boxes created. In the example below, you can see how this is done for the aforementioned example. The important thing to notice is not that it classifies the classes perfectly (this is trivial and may just as well be a case of overfitting), but that the shape of the resulting areas seem to capture the shapes of the point sets, and thus might just to be able to classify new points in the same space.



The Automatic Tree Learning Anomaly Segmentation (ATLAS) method makes a decision tree from a 4 dimensional point set (the dimensions being DWI-value, ADC-value, mirror corrected DWI-value and mirror corrected ADC-value) and an expert drawn core DWI lesion. The decision tree is used on data from other patients (than the ones used to build the tree), to make a prediction of whether a voxel is in the core lesion or not. As any other supervised learning method, a decision tree is prone to overfitting, so to counteract this, the resulting prediction is smoothed and morphological corrected, taking advantage of the available, though hitherto unused locational data.

The result is a superb segmentation of the core lesion. The process can be seen in the figure on the right:



NEUROINFORMATICS

Cerebral Cancer Imaging Research

By Mikkel Bo Hansen, Leif Østergaard, Sune Nørhøj Jespersen and Kim Mouridsen

Technological Foundation

Disturbed capillary morphology or regulation of microvascular flow, so-called capillary dysfunction, is speculated to form the underpinning of many diseases. During recent years, researchers at CFIN, pioneered by Leif Østergaard, Kim Mouridsen, and Sune Nørhøj Jespersen, have developed techniques for measuring markers of capillary dysfunction from non-invasive imaging data from MRI and CT based perfusion measurements. These techniques model the passage of a vascular tracer in terms of a voxel specific distribution of capillary transit times, which in itself may hold valuable information, but also form part of the base for allowing prediction of tissue oxygenation.

Algorithms for reliably estimating the distribution of transit times continue to be a cardinal point of research. In 2006 (Mouridsen, Friston et al. 2006) and 2014 (Mouridsen, Hansen et al. 2014), algorithms for imaging a closed vascular network (i.e. the tracer needed to be constrained to the vasculature), was published and adapted by the scientific community. In 2016, CFIN researchers published an extended model (Hansen, Tietze et al. 2016), with the capability of measuring tissue oxygenation also in the presence of contrast agent extravasation, which is crucial in diseases such as cerebral tumors (glioma), multiple sclerosis, and adrenoleukodystrophy (Lorenzo's oil disease), which are characterized by their disrupted blood-brain-barrier. Applied to 60 glioma patients, the methodology displayed significant separation of affected tissue versus unaffected tissue, a significant improvement over traditional perfusion markers.

Collaborators and Selected Studies

Our research continues to attract interest from leading research groups in the EU and US, of which notable institutions include Harvard Medical School, Massachusetts General Hospital, Charité Berlin, Hamburg-Eppendorf University Hospital, Heidelberg University, and the University of Erlangen-Nürnberg.

In Figure 1, transit time distribution and metabolic markers are presented for a glioblastoma patient before and after treatment with a drug that inhibits the tumors ability to form new microvessels. In this case, the patient responded well to treatment and displayed no disease progression for 18 months, which is quite uncharacteristic for this aggressive disease. Indeed, the monitoring of treatment response seems to be a major potential of the methodology.

Collaborators in Heidelberg successfully demonstrated that tumors, which had lower metabolic rates of oxygen as predicted by our method, responded better to treatment and lived longer ($p<0.01$) compared to more metabolic active tumors (Bonekamp, Mouridsen et al. 2016).

Similarly, collaborators at University of Erlangen-Nürnberg were able to show that transit time distribution parameters could distinguish recurrent glioblastoma from newly occurring glioblastoma (Stadlbauer, Mouridsen et al. 2017).

In a 2015 paper, CFIN researchers were able to show that capillary dysfunction markers (capillary transit time heterogeneity - CTH) in conjunction with the traditional cerebral blood volume (CBV) predicted tumor grade, outcome, and adverse events up to 20% more accurately compared to traditional methodology (Tietze, Mouridsen et al. 2015).

In conclusion, despite being a relatively 'young' technology, the novel way of analyzing perfusion data has spawned great interest and provided clinically valuable results already.

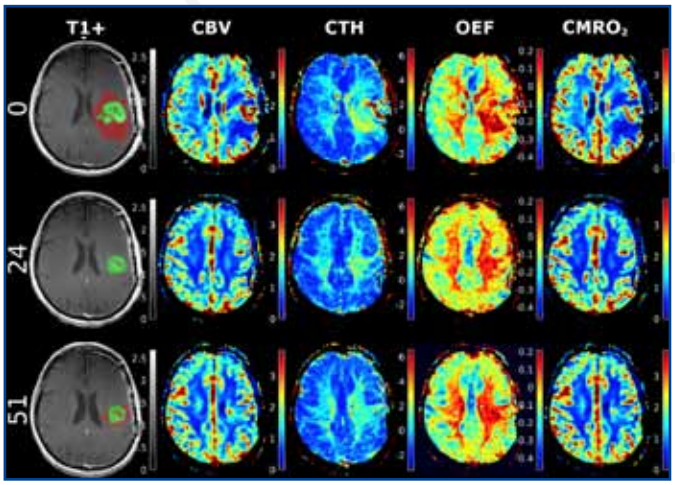


Figure 1
Sample images from a patient before (0) treatment and 24 and 51 days after treatment initiation. The patient displays almost complete reduction of peri-tumoral edema (red area on T1+ images) and no discernible growth of tumor core (green area on T1+ images). This is parallelled by normalization of CBV, CTH, and OEF and, quite notably, the metabolism ($CMRO_2$) is almost completely normalized following treatment.
Images: T1+: Post contrast T1 image, CBV: Cerebral blood volume, CTH: Capillary transit time heterogeneity, OEF: Oxygen extraction fraction, and $CMRO_2$: Cerebral metabolic rate of oxygen.

Further Developments

The visualization of tissue oxygenation status holds many interesting perspectives from research as well as clinical applications. Further characterization of such methods is important and currently undergoing, using leverage from the many international collaborators approaching CFIN/MIND*Lab*.

Two primary future research directions are currently being pursued. First, much of the research within novel metabolic biomarkers is applicable only in the context of closed vascular networks, that is, a reasonably well-functioning blood-brain-barrier. This limits the applicability of our previous method developed for the brain (traditional T2-weighted perfusion MRI). Hence, future research is targeted at developing biophysical models for T1-weighted perfusion, which is applicable not only to brain, but to all organs. Second, the successes obtained so far with our novel imaging biomarkers gives hope that these images may enrich the disease information available from individual patients when combined with Deep Learning, for example artificial neural network (ANN) technologies. We are currently pursuing this technology with the aim of predicting response to treatment very early guiding earlier shift in treatment strategy based on such analysis.

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NEW FACE at CFIN

Michelle Livne, MSc (Neuroscience)

Michelle accomplished her Bachelor in biomedical engineering at the Technion, Haifa, Israel. Her master took place at the center for stroke research (CSB) of Charité Universitätsmedizin Berlin (Jan Sobesky) in collaboration with CFIN (Kim Mouridsen) with a thesis entitled "Automated MRI perfusion map acquisition - a multimodal PET and MRI study".

Afterwards, Michelle was employed by the CSB as a research assistant.

In June 2015 Michelle started her PhD studies in a collaborative project of the CSB (Jan Sobesky and Jochen Fiebach), CFIN (Kim Mouridsen) and the Technion (Ronen Talmon). The PhD project, "MRI for Stroke StratificatION" (MISSION) focuses on developing MR-based statistical tool for acute stroke patients stratification in the clinical settings. The promising results of this collaborative research yielded two publications thus far.

Michelle's research interests are in building machine learning applications to benefit healthcare. Her main focus is on developing predictive models based on clinical information and imaging data.

NEUROINFORMATICS

Deep learning

by Anne Nielsen, Mikkel Bo Hansen and Kim Mouridsen

Deep learning: Utilizing the potential in data bases to predict individual outcome in acute stroke

Acute ischemic stroke is one of the major diseases responsible for adult death and severe disability. Accordingly, one third of the 15 million annual incidents worldwide leading to death and another third leading to permanent disability. Brain tissue is permanently damaged within hours, and rapid reperfusion by endovascular and/or thrombolytic treatment is therefore of utmost importance for good outcome. The therapeutic strategy is today based on images of the brain obtained from either computed tomography (CT) or magnetic resonance imaging (MRI).

During the last 10 years, many attempts have been made to optimize and automate treatment decisions in stroke, but most have been based on time from onset, or on simple, population-wide imaging thresholds.

Stroke evolution is physiologically highly complex and we are therefore taking a different approach based on novel advances in so-called *deep learning*. In particular, a branch called artificial neural networks (ANN) is now a technique with promising applications in both science and everyday life, currently promoted by strong research groups associated with companies such as Google, Facebook, and Netflix.

Broadly speaking, an ANN mimics the neuronal circuitry of the human brain, thereby facilitating efficient encoding of complex imaging patterns at increasing levels of abstraction.

During 2015-2016 we have developed an ANN[1] to predict the final outcome of acute ischemic stroke based on a large database of MRI scans. We have shown that exact stacking of simple structures in to deep networks catalyzes the model's learning ability, whereas shallower architectures fail to capture the underlying stroke dynamics, see Figure 1 for an architectural overview and Figure 2 for a comparison which also includes the current state-of-the-art method[2, 3]. Predictions are based on mean transit time (MTT), the cerebral metabolism of oxygen[4] ($CMRO_2$) and the apparent diffusion coefficient (ADC).

The comparison of predictive models shows a clear advantage of using a deep ANN to produce prediction of final infarct in acute ischemic stroke. Even a shallow ANN has the advantages of being able to retain non-linear information, making its predictions more accurate compared to a traditional logistic regression based method. The depth of the convolutional neural network is important, as more layers in the network yield a better contrast of the predicted images. The new model paradigms will lead to improved predictions and thereby potentially personalized treatment and better outcome for the individual patient.

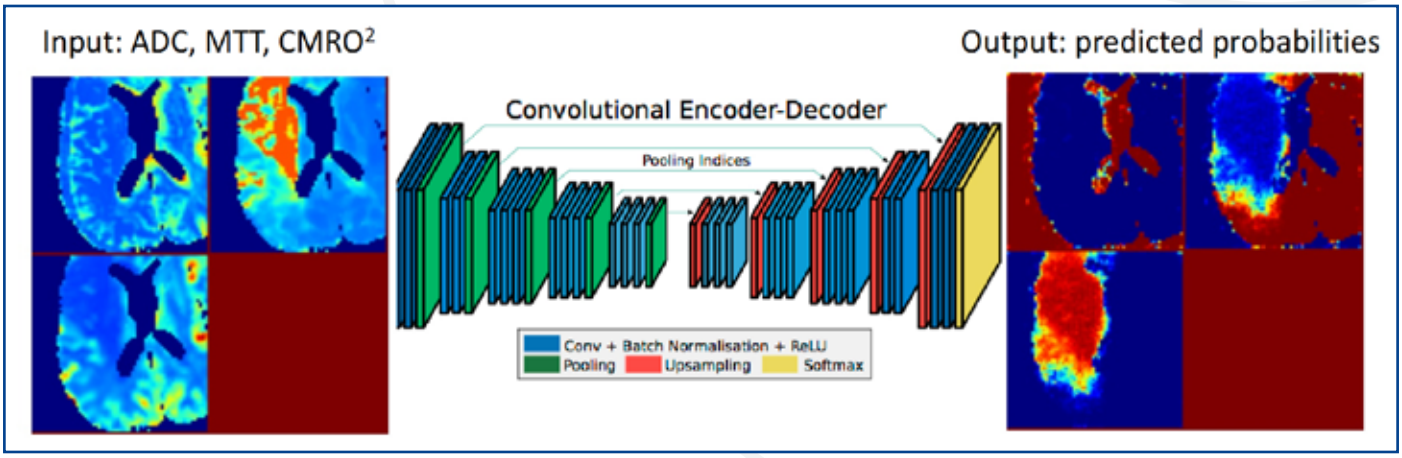

Figure 1
Schematic drawing showing the architecture of the very deep ANN. Every slice in the middle figure corresponds to a layer in the network. On the left, the input used in the algorithm (ADC, MTT and CMRO2). On the right, the outcome of the network is the probabilities of pixels being non-tissue, healthy tissue and infarcted tissue.

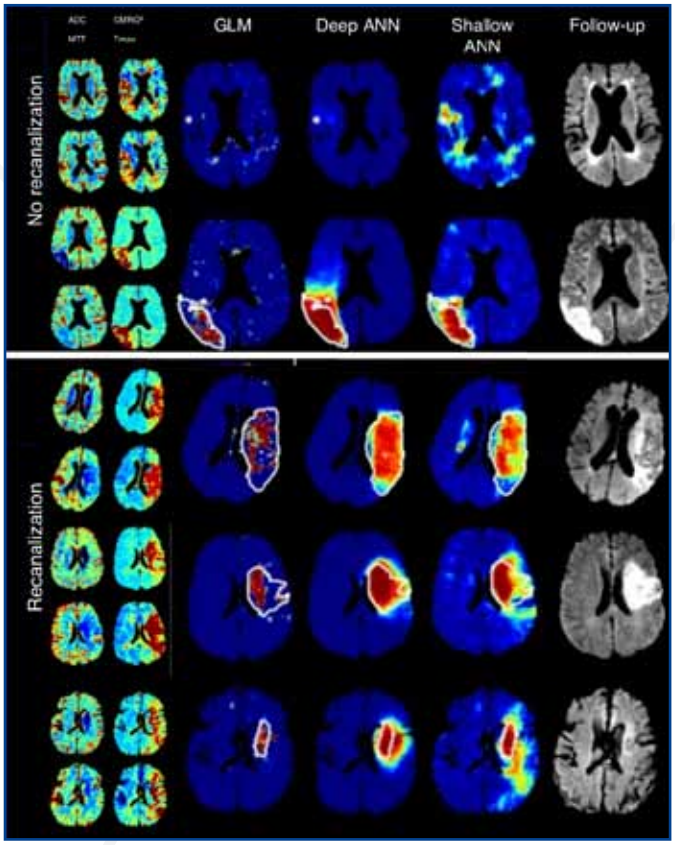

Figure 2
Results from the three different predictive algorithms; a conventional method based on logistic regression, a very deep ANN, and a shallow ANN. Left column shows imaging biomarkers (ADC, CMRO2 and MTT used as predictors and Tmax), and right column shows the results from the follow-up scan.

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NEW FACE at CFIN

Anne Nielsen, MSc (Statistics).

Anne completed her master in collaboration with CFIN (Kim Mouridsen) and Department of Mathematics (Jens Ledet Jensen) with a thesis entitled "New Methods for Finding Event Related Brain Activity Using fMRI".

Afterwards, Anne was employed as a Research Assistant at CFIN and Combat Stroke in October 2015.

Anne's work has been focused on the use of artificial convolutional neural networks to predict the final outcome of acute ischemic stroke. She has conducted a pilot study (described on these pages) showing promising results compared to existing state-of-the-art methods. Additionally, she has assisted other CFIN researchers in data analyses, while at the same time finalizing the promising work from her Masters project for publication in collaboration with Kim Mouridsen and Torben E. Lund.

In the beginning of 2017, Anne will start as an Industrial PhD student at Combat Stroke and CFIN. The project is entitled "Convolutional Neural Network Based Prediction of Acute Stroke Response to Treatment" and will focus on further development of the artificial neural network from the pilot study.

The Industrial PhD project is jointly funded by Combat Stroke and Innovation Fund Denmark.

Combat Stroke

Innovation Fund Denmark

CFIN / MIND*Lab*

MEG continues to grow at CFIN

by Yury Shtyrov

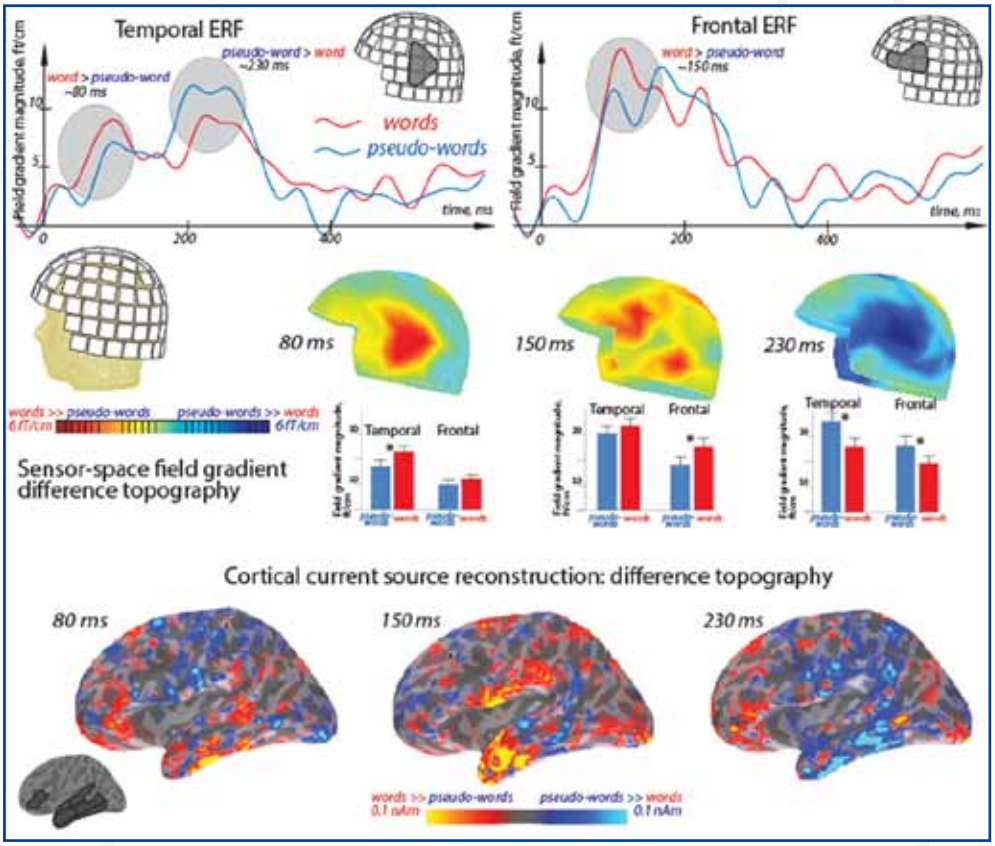
During the past years, the MEG Laboratory has seen a lot of new developments. A major upgrade that took place in 2015-2016 was an installation of a helium recycler. Weekly refills of liquid helium, needed to ensure the superconductive properties of MEG sensors, were replaced by a recycling procedure which re-uses the gas present in the system by extracting gaseous helium, re-liquefying it on-site and pumping it back into the dewar. Since its installation, the recycling system has proved to be an asset to the lab; it dynamically estimates the needs and uses any available gaps in the recording schedule to refill the dewar without any human intervention. This has both dramatically cut the costs of helium supply and reduced the downtime related to the lab maintenance. The funds saved on helium could, in turn, be redirected to other lab and CFIN needs.

The stimulation and recordings systems have seen various upgrades improving their overall quality. The previously added customised EEG layout has now been complemented by a bespoke EEG impedance measuring system. Over 2013-2014, we started to routinely use combined EEG/MEG recordings, providing high-quality data simultaneously in both of these modalities, which greatly improves spatial resolution of source estimates. That, however, introduced the needs to mount EEG caps on individual subjects and to measure the quality of signal conduction ("impedance") between the head and the electrodes, something that the default set-up was not ideal for. This has now been resolved with an introduction of a custom-made electrode-impedance measurement system that has become instrumental in streamlining recordings and shortening preparation times. The most noteworthy of new stimulus delivery devices is a state-of-the-art PROPixx projector optimised for vision research, which was installed in 2016. It is capable of precisely timed presentation of colour-calibrated full-HD images at an impressive 480 Hz refresh rate, and up to 1440 Hz in grayscale. When interfaced to the already installed high-resolution eye-tracking device in the MEG lab, whole new avenues of study are opened into both basic visual processing as well as higher-order visual cognition.

A very important activity at the MEG Lab has been a series of seminars and training events dedicated to raising the level of methodological expertise in MEG research at Aarhus

MEG - magnetoencephalography

One of the state-of-the-art brain imaging facilities actively developing at CFIN is magnetoencephalography, or MEG. The MEG technique can monitor brain activity with a high temporal resolution (with sub-millisecond precision), which it does by recording instantaneously miniscule magnetic fields generated by electric currents in neurons, the brain's main working cells. These tiny magnetic fields are picked up by the so called super-conductive quantum interference devices, SQUIDS, sophisticated miniature sensors, which are distributed around a person's head in a helmet-shaped device and kept at super-low temperatures near the absolute zero. As the magnetic fields permeate through human tissues and air, there is no need for a solid conductor between the head and the measuring device, which makes MEG recordings much more convenient and time-efficient for both subjects and researchers. The technique is quiet and non-invasive: the recordings do not involve any currents, fields or substances "injected" into the participant's body, the operation is completely silent with participant seated in a comfortable chair in a spacious magnetically-shielded room. As MEG allows for more direct estimates of electrical activity sources in the brain, it enables analysis of not only the timing but also of the spatial location of neuronal activation, thus showing in real time the complex interplay of various brain areas as they are processing the information coming to our central nervous system. The Triux™ MEG device donated by the VELUX and VILLUM Foundations, and installed at CFIN, is a masterpiece of state-of-the-art technology produced by Elekta Neuromag (Helsinki/Stockholm), an international leader in biomedical technology. It incorporates 306 MEG sensors of different types making it capable of high resolution in different spatial dimensions; these are complemented by continuous head position tracking, 128 EEG channels and other data outputs which altogether can yield the most accurate spatial-temporal image of the brain activity currently possible. CFIN's MEG Laboratory is the first installation of its kind in Denmark and Scandinavia.



Spatio-temporal patterns of neural processes underlying visual word comprehension. MEG experiments demonstrate a neocortical signature of automatic near-instant access to word representations in the brain: rapid neural dynamics that arises in the temporo-frontal language network between 70 and 250 milliseconds after word presentation. Adopted from: Shtyrov Y. & MacGregor L J. Near-instant automatic access to visually presented words in the human neocortex: neuromagnetic evidence. Sci. Rep. 6, 26558; doi: 10.1038/srep26558 (2016).

University, increasing the awareness of MEG in the Danish neuroscientific, clinical and psychological communities and building stronger international collaborative networks. This included various training workshops dedicated to data analysis, as well as a series of invited talks by international leaders in MEG and EEG research. All of these events have been a large success and attracted national and international audience.

Finally, and most importantly, the MEG lab has seen an influx of new users and new experimental and clinical recordings during the past two years. This includes large-scale projects on language acquisition in adults and children, development of paradigms for assessment of consciousness disorders, investigations into Parkinson's disease, as well as studies of music perception and olfactory processing. Among others, the MEG user group was expanded in 2016 by the arrival of Associate Professor Sarang Dalal and his group, whose innovative ERC-funded research on vision will use a combination of neuroimaging and electrophysiological methods. Several sophisticated image processing circuits have been discovered in the animal retina, but to date, studies of complex visual function in humans has been restricted to cerebral cortex. By measuring electroretinography (ERG) together with MEG, his team will examine in detail how visual information is encoded and communicated across the entire visual pathway in humans, including between the retina and cerebral cortex. The millisecond-precision required for these experiments have been made possible with the installation of the new PROPixx projector into the MEG lab.

Ongoing research includes multiple other projects dealing with various cognitive and clinical questions, while the MEG is also routinely used for clinical diagnostic purposes, most importantly for pre-surgical mapping in epilepsy patients.

NEW FACE at CFIN

Nikola Vukovic is a new postdoctoral researcher at CFIN, working with Dr Yury Shtyrov in the Laboratory of NeuroDynamics of Human Communication (NeDComm Lab) since October 2015.

He holds a PhD in Cognitive Neuroscience from the University of Cambridge, and studies how our brain lets us acquire, use, and communicate meaning through the medium of language.

Most recently, Nikola has worked on a Lundbeck Foundation-funded project, where he uses combined TMS, fMRI, DKI, and behavioural methods to identify the spatial profile and causal role of early microstructural brain signatures of word learning.

NEW FACE at CFIN

Christelle Gansonre, M.Phil (Linguistics, Oxon.), has been working on a PhD project entitled *Speech as an index of consciousness* under the supervision of Professor Yury Shtyrov and Professor Morten Overgaard since December 2014.

After completing a master in linguistics, she worked as a research assistant at the Language and Brain Lab, University of Oxford, on an EEG project investigating structural predictions during online sentence processing.

At CFIN, Christelle is working on a M/EEG project investigating possible ERP markers of language processing in patients with disorders of consciousness funded by The Lundbeck Foundation.

NEW FACE at CFIN

Rasha Hyder, MSc (Electrical and Electronics Engineering), PhD student at CFIN since April 2016 with Yury Shtyrov. She received her MSc on the topic of "Mapping of language brain areas in patients with brain tumours using MEG" from Universiti Teknologi Petronas, Malaysia.
Rasha is working on her PhD project entitled "Neural foundations of language processing deficits in Parkinson's disease and their modulation with deep brain STN stimulation: neuro-magnetic investigations"
Rasha is using combined EEG/MEG to investigate the time course of neural activations related to the processing of different linguistic aspects. MRIs are used to estimate the neural sources of measured E/MEG signals.

Flavour Institute

by Therese Ovesen

In the Flavour Institute, we aim to advance the knowledge of smell, taste, and how these merge in flavour. A loss of sensory abilities will often reduce quality of life, but may also be an earlier warning sign of psychiatric, neurologic and neuro-degenerative disease. By involving all aspects of smell, taste, and flavour, we work to form a platform for a multidisciplinary approach in research, clinical diagnostics, and treatment.

The research activities within the framework of Flavour Institute are organized in three domains: a model-based domain, a pre-clinical domain, and a clinical domain. The institute comprises a board of directors with three members, each of whom is not only responsible for a specific domain, but also for the interaction and communication between domains. Furthermore, we are very proud of our advisory board which counts many internationally renowned and prominent flavour researchers. Several PhD and post doc courses have been initiated, engaging medical doctors, bio-medical engineers and psychologists who manage a broad spectrum of techniques and methods, from cultivation of olfactory stem cells over behavioural taste and smell tests, to computational modelling of the brain. The effort so far has been to provide baseline and normative data for olfaction whereas our present focus is gustatory function and studies on both smell and taste disorders associated with a variety of diseases. Finally, we aim to unravel changes induced by intensive taste and smell training – knowledge that is intended to be included in future rehabilitation programs for patients suffering from dysfunctional flavour senses.

The Flavour Clinic

Evaluation of olfactory functions is essential in the evaluation of patients with olfactory disorders and prior to nasal surgery, in order to guide therapeutic intervention and to assess the effect of surgery. Olfactory assessment is regarded an essential part of the oto-rhino-laryngologic examination in patients with nasal or sinus diseases and is being used as a supportive diagnostic tool for neurological disorders. In collaboration with the Department of Otorhinolaryngology, Holstebro Regional Hospital, Central Region Denmark, we opened the first outpatient clinic for diagnosing and treating patients with olfactory or gustatory deficits in Denmark in December 2016. In a close collaboration between clinicians and researchers, we are working to deliver the best possible clinical care for patients with chemosensory deficits. Here, we integrate the latest knowledge achieved through the model-based and the pre-clinical flavour studies conducted in Danish NeuroScience Center (DNC) – to complete the research circuit from basic science to patients - and back.

Researchers Henrique Fernandes and Alexander Fjældstad conducting MR scans

Announcement of the opening of the new Flavour Clinic in Danish national TV2, December 2016

Professor Therese Ovesen in the lab

Researchers Alexander Fjældstad and Henrique Fernandes in the lab

NEMO

Neuroelectromagnetic Oscillations (NEMO) Group

by Sarang S. Dalal

The retina as a window to the brain

The retina is known to substantially preprocess visual stimuli, and many neuroscientists consider it to be an extension of the brain due to the sophistication of its neural circuitry. The electrical activity of the retina, or the electroretinogram (ERG), can be measured using special electrodes placed on or near the eye. While this technique has long been used to study retinal neurophysiology in animal models and is even in routine clinical use to diagnose retinal dysfunction in vision-impaired patients, its application to vision neuroscience research in humans has been exceedingly rare. This is a rather crucial oversight, as we now know that the retina contains circuitry that carries out quite sophisticated processing on visual scenes – even including detection of moving objects – before transmitting information to cerebral cortex. Indeed, since the turn of the millennium, the retina has enjoyed a revival of sorts in neurophysiology (Gollisch and Meister, 2010). It turned out that the latest concepts in neural synchrony and information processing applied equally well to investigating retinal function.

The retina has long been known to generate a high-frequency burst called the *oscillatory potential* in response to visual stimuli. These fast rhythms are thought to arise from amacrine cells and ganglion cells – which send their outputs to visual cortex via thalamus. Originally, these responses were thought to occur at different frequencies than gamma band responses in visual cortex (Heinrich and Bach, 2004), but ultimately this may have turned out to be a limitation of scalp EEG, as both MEG (Muthukumaraswamy and Singh, 2013) and intracranial EEG (Vidal et al., 2010) have now been shown to be more sensitive to these higher-frequency responses in visual cortex. Indeed, in electrophysiological experiments in cats, high-frequency retinal oscillations appear to drive a channel for carrying information via the lateral geniculate nucleus to visual cortex (Koepsell et al., 2009). Yet, whether the retina may directly drive signals of similar frequency in visual cortex has not been further explored in humans.

In our initial experiments, we aim to characterize the basic neural responses to simple light flashes across the visual pathway from retina to cortex. In a first experiment, we employed brief light flashes of only 1 ms duration, made possible with the installation of a PROPixx projector into the MEG lab, while we simultaneously measured ERG and MEG signals from our participants. We particularly examined high-frequency responses (~115 Hz) in the ERG with respect to the corresponding responses of thalamus and visual cortex, as reconstructed from MEG data.

We found that the retinal oscillatory potential evoked by these flashes occur after 20 milliseconds, while the first MEG responses already occur at approximately 25 milliseconds. They appear to originate from the lateral geniculate nucleus and pulvinar regions of the thalamus, which are structures that are considered challenging to examine with noninvasive techniques. Finally, responses in primary visual cortex and associative areas commence around 30 ms, i.e., within 10 ms after the retinal oscillatory potential and following the thalamus by about 5 ms. This timeline of events is actually quite a bit faster than EEG researchers typically consider, but agrees better with electrophysiological studies in other species.

Our results support the view that high-frequency modulations reflect the precise timing of information handling in both cortex as well as its afferents: the timing of the ERG oscillatory potential indeed suggests that it arises from the output stages of the retina, a plausible thalamic response occurs only a few milliseconds later, and finally after another short delay, a massive cortical response appears in several structures in primary and higher-order visual cortex. These high gamma band responses occurred much earlier than the classic visual evoked response, with initial brain activity detected already between 25-35 ms. Measuring ERG together with MEG may therefore provide a more informative measure of information processing at each stage of the visual pathway, and potentially provide improved diagnostics to discover disturbances of the visual pathway in disease.

In a second experiment led by my PhD student and soon-to-be CFIN postdoc Britta Westner, light flashes of longer duration (about half a second) were employed to additionally examine retinal and cortical responses to the disappearance of light. The visual system appears to process darks faster than lights, evidenced both by cortical measurements and reaction times (Komban et al., 2014). However, it is unknown whether the retina itself or the thalamus could contribute to this faster speed of processing. The retina does produce a well-known evoked response at the transition from light to dark, though high-frequency responses have never been reported in this situation. We hypothesized that, using analysis techniques that are now common in MEG and EEG, high-frequency responses would be revealed in the retina also when lights turn off, prior

to corresponding cortical responses. Our preliminary results indicate that this is indeed the case, with responses to the disappearance of light occurring earlier and in a slightly lower frequency (around 85 Hz) than the transition from light to dark (115 Hz). The timing of the retinal responses between the two situations appears to be similar, while cortical responses are indeed faster for darks, suggesting that the thalamus or the optic tracts themselves are responsible for relaying darks more quickly.

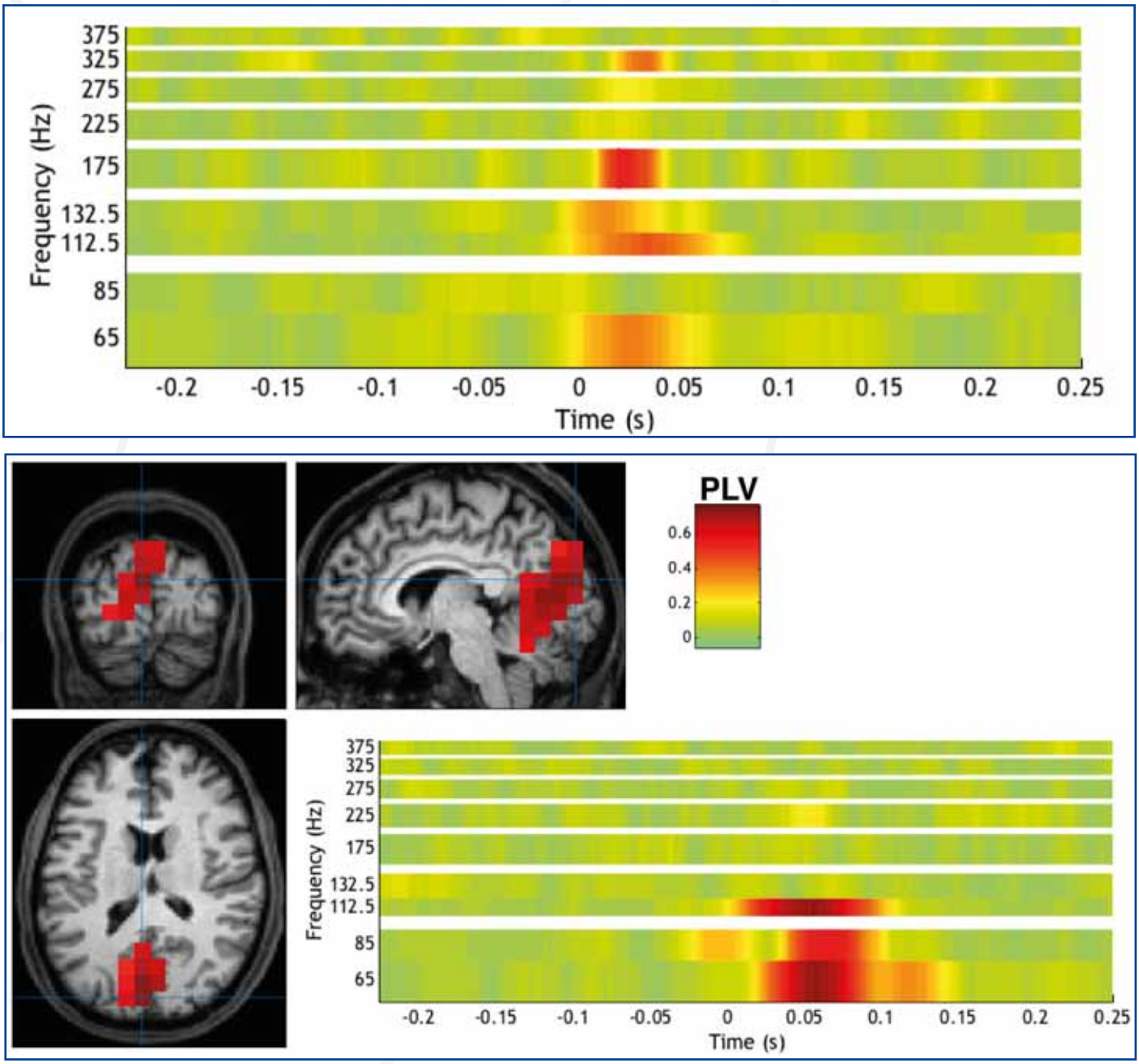


Figure 1
(a) The degree of phase-locking, a measure of neural synchronization, in the retina as measured by the ERG, across time and frequency.
(b) The corresponding cortical synchronization map derived from MEG and overlaid on a structural MRI, demonstrating activity in visual cortex. Cortical synchronization in the 115 Hz band follows the retina. Using this technique, we expect to be able to measure how retinocortical propagation times change under a variety of conditions, as well as further examine whether the particular frequencies involved in retinal synchronization drive the corresponding frequencies observed in visual cortex.

A camera dome for fast and accurate measurements of MEG coils and EEG electrodes

Measuring the locations of MEG sensors and EEG electrodes on the head is a necessary procedure for neural source localization, i.e., determining precisely which brain structures generated which signals. This is typically performed using an electromagnetic or infrared digitizer system; however, the procedure is relatively cumbersome, time-consuming, and ultimately, less accurate than one would hope. In fact, the measurement errors are sufficient to impair source localization performance and possibly prevent the detection of weaker or deeper brain sources (Dalal et al., 2014).

Figure 2a
Custom-built dome containing an array of 35 digital cameras, located in CFIN's MEG laboratory.

However, the proliferation of affordable digital cameras has made feasible an affordable, faster, and more accurate solution: by taking photographs of a subject from a variety of angles, a 3D computer model of it can be created using a technique called *photogrammetry*. This strategy has been used to create several familiar 3D applications, such as the 3D views of buildings featured in Google Maps and the iconic "bullet time" sequence featured in the film *The Matrix*.

With the aim of measuring the positions of MEG coils and EEG electrodes, our research assistant, Tommy Clausner, spent the summer constructing a dome containing an array of 35 cameras (Figure 2a). This included writing the software to control it and assemble the resulting data (Figure 2b), which is now released as the open source *janus3D* (available at https://janus3d.github.io/janus3D_toolbox/).

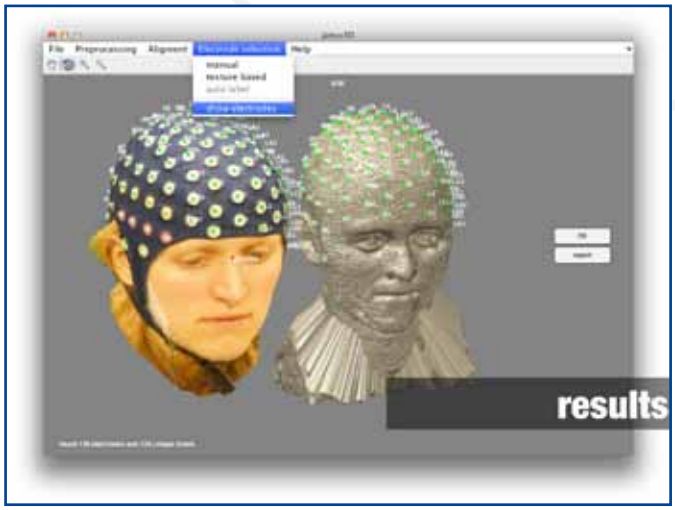


Figure 2b
Screenshot of janus3D showing a 3D reconstruction derived from photographs of a volunteer wearing an EEG cap (left) and the corresponding electrode locations matched to the volunteer's MRI scan (right).

The acquisition procedure will greatly shorten preparation time for each MEG and EEG session, while the post-processing of the images will be less error-prone than the current MRI coregistration procedure and ultimately result in more reliable neural source localization. A participant simply stands underneath the dome, after the MEG coils or EEG cap have been fitted. In an instant, the cameras simultaneously capture

all 35 different viewpoints around the head, and the participant is then immediately ready for the MEG or EEG recording. Offline, the different photographs are assembled into a 3D representation of the participant's head, together with the MEG or EEG positions. The participant's facial landmarks are then semi-automatically matched to their corresponding structural MRI, yielding the precise coordinates of the MEG sensors or EEG electrodes relative to the brain.

We greatly look forward to integrating the camera dome into our standard laboratory protocol for MEG and EEG recordings.

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NEW FACE at CFIN

Sarang S. Dalal, Associate Professor.

Sarang joined the Center of Functionally Integrative Neuroscience in March 2016 and is the leader of the Neuroelectromagnetic Oscillations (NEMO) group.

Sarang grew up in the San Francisco and San Diego areas, and completed his BS in Biomedical Engineering at Johns Hopkins University (2000). He returned to the Bay Area to earn his PhD in Bioengineering at UCSF and UC Berkeley (2007).

He then went to the Brain Dynamics and Cognition Lab at the Lyon Neuroscience Research Center in France, on what was initially to be a 1-year Chateaubriand Fellowship. A Marie Curie Fellowship prolonged his stay there until starting a junior research group leader at the University of Konstanz in Germany (2011).

His research interests concern primarily the role of neural oscillations both in healthy cognitive function and in disease, as well as pushing the limits of both MEG and EEG with methods development. Incorporating the latest structural MRI techniques has been integral to this work.

Throughout his research career, he has leveraged magnetoencephalography (MEG) along with intracranial EEG recordings to gain a better understanding of cortical oscillatory dynamics, particularly in high frequencies, and have recently launched new lines of research into the human theta and alpha rhythms. Another project nearing completion brought together his loves of neuroscience and bicycling, investigating how disturbances in the high-frequency oscillations of the basal ganglia in Parkinson's disease often result in difficulties walking but not pedaling a bicycle.

He recently began a new line of research through an ERC Starting Grant. The project aims to characterize in detail how neural oscillations in the human retina code visual information and facilitate communication with cerebral cortex for further processing. This will primarily use electroretinography (ERG) and MEG together to examine the flow of high-frequency oscillations in the visual pathway.

Hedonia Research Group

Hedonia and eudaimonia in the brain

by Morten L. Kringelbach

In Hedonia we continue to draw inspiration from the ideas of Aristotle, who proposed that the good life consists of hedonia (hedone, the ancient Greek word for pleasure derived from the sweet taste of honey, hedus) and eudaimonia (a life well-lived)[1].

Hedonia is based at both Aarhus and Oxford, and we are embedded within Music in the Brain centre to use music as a perhaps uniquely human way to engage and reveal the underlying, core brain processes constituting and underlying emotion[2-6]. We have strong collaborative links between Aarhus, Oxford and Barcelona which enable us to combine methods from a number of disciplines including psychology, neuroscience, physics, engineering and computer science to create groundbreaking science.

Whole-brain methods

Aristotle has not only been an inspiration in terms of studying the pleasure, but also in the development of our novel whole-brain computational methods. Specifically we have drawn inspiration from the ideas of the medieval philosopher Thomas Aquinas who, in the spirit of Aristotle, wrote "Quidquid recipitur ad modum recipientis recipitur", i.e. the container (or recipient) shapes the content.

Together with my close collaborator Prof Gustavo Deco (Barcelona, Spain), who holds the ERC Advanced grant DYSTRUCTURE, we have started to explore this dynamical, causal relationship between the brain and its content. We are building whole-brain computational models that take their inspiration from the Aristotelian idea of how containers shape content or how spontaneous brain activity must be tied to the underlying structure of the anatomical connections linking them. In a series of state-of-the-art studies we have demonstrated that these dynamical models can describe the spontaneous or intrinsic activity of the brain with high accuracy [7-10].

Further to this simple structural insight, it has become very clear that time plays a crucial role in the human brain, giving rise to the time-critical neural computations allowing organisms to survive[10]. The complex brain activity during rest and cognition plays out on the background of the brain's structural connectivity, and crucially has to balance the exploration of this dynamical potential to ensure stability in the long-term. We have shown that the brain has to balance integration and segregation processing in order to function optimally[9].

We have developed methods to extract the anatomical structural skeleton of the individual brain, i.e. the structural connectivity (SC) that can be expressed in terms of a structural connectivity matrix. This can be mapped *in vivo* in humans on the scale of millimetres using diffusion weighted/tensor imaging (DWI/DTI) which can measure the white-matter fiber tracts constrained by the diffusion of water molecules and where the connectivity between brain regions can be reconstructed by probabilistic tractography.

Whole-brain computational models combine brain structure and activity dynamics to explore and explain the emergence of resting-state networks mechanistically. Until recently, the models have typically been either oscillatory or asynchronous. These models use different strategies to explain the functional connectivity of the data over time, either, in the case of oscillatory models, by maximizing the metastability of the dynamics, or, in the case of asynchronous models, by working at the border of multistability, i.e. at a dynamical point at the edge of the bifurcation where the trivial spontaneous state loses stability.

The stability of whole-brain computational models hinges on different concepts from dynamical systems. The asynchronous models provide evidence that the simulated functional connectivity best matches empirically observed functional connectivity when the whole-brain network is subcritical, meaning that when there are stable attractors states, with a spontaneous state with low activity in all regions, and several excited states with high activity between selected regions. In other words, multistability around a spontaneous state defines an operating point such that system activity stochastically explores the dynamic repertoire inherent to the structural connectivity.

Similarly, the oscillatory models provide evidence for the importance of metastability, which is a measure of how variable brain states are as a function of time; e.g. how the synchronization between the different brain regions fluctuates across time. These concepts of multi- and metastability for describing the dynamical systems in the brain are possible scenarios for the resting state. It remains an active area of research to determine which is a more accurate description.

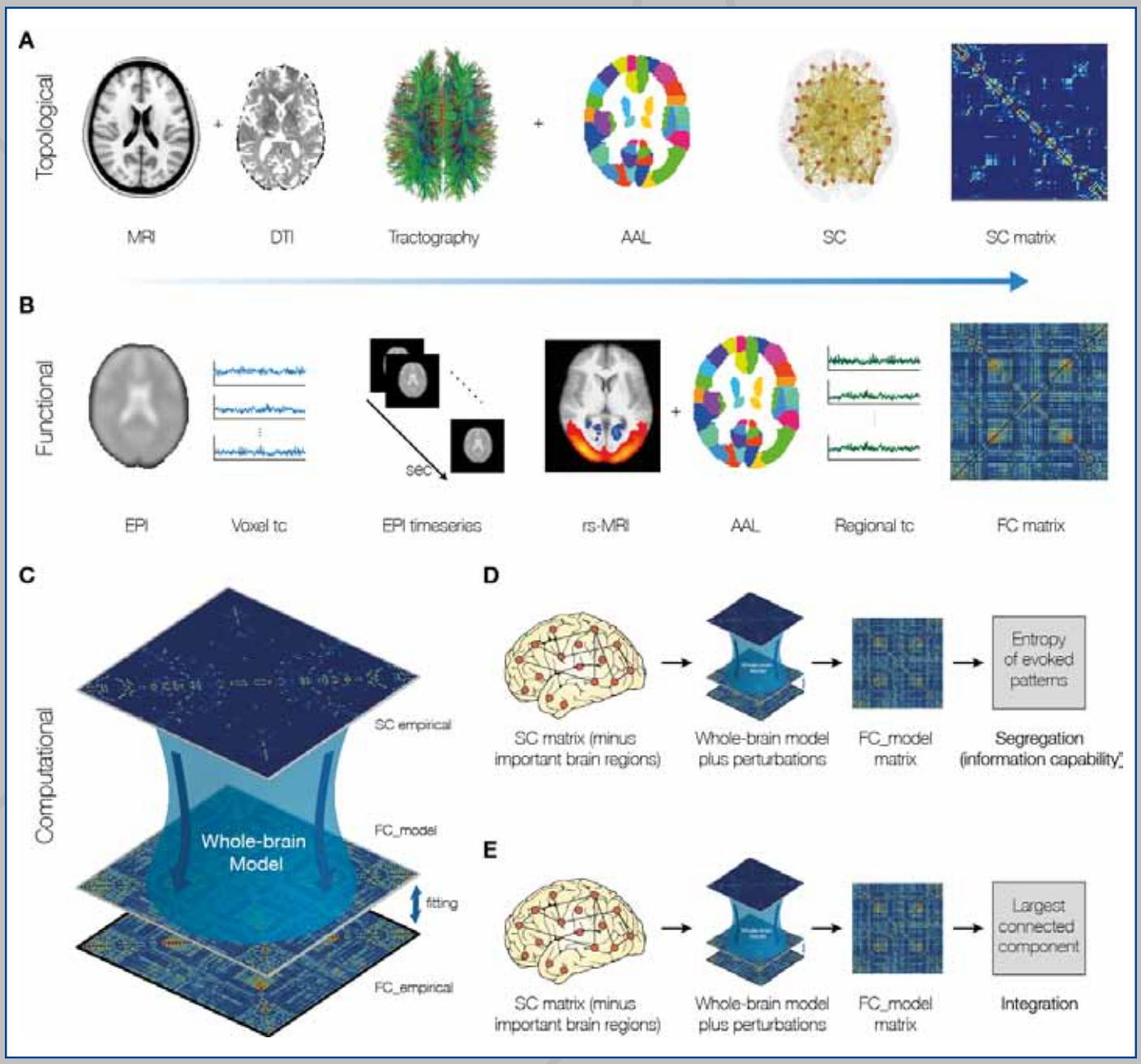

Figure 1
Overview of whole-brain computational connectomics.
A) First extract the container, ie the topological measure of the structural connectivity (SC) matrix by combining structural MRI, DTI, a given parcellation scheme and tractography.
B) Then derive the content, ie the functional connectivity (FC) matrix by extracting the BOLD resting state data with the AAL parcellation and correlating the time courses.
C) Combine the structural and functional data by fitting this to a whole-brain computational model.
D) This model can be used to estimate the causal influence of individual regions by computing the segregation (or information capability) of a given SC as the entropy of the set of evoked patterns assuming a Gaussian distribution averaged over a large number of external stimulations.
E) Similarly, the model can be used to estimate the integration as the length of the largest connected component in the functional connectivity matrix, averaged over a large number of external stimulations.

Further, we have recently demonstrated the potential for using whole-brain computational modelling for revealing causal brain mechanisms[11]. We introduced a promising new measure of binding in the human brain, by which brain regions are ranked according to their level of temporal integration. We were able to lesion the model to demonstrate a causal relationship between these binding regions and brain activity.

Parental brain

We are using these techniques in the ERC funded CAREGIVING five-year project to help understand the mechanisms underlying parental caregiving. Over the first 2 years, we have made significant progress in elucidating the underlying mechanisms of parent-infant caregiving. In addition, these new tools have also helped shed new light on pleasure and reward processing in the human brain. In total, this research has so far given rise to 25 peer-reviewed articles of which I highlight some of the main findings related to caregiving below.

In terms of the underlying brain mechanisms of caregiving we have published a recent review in the high-impact journal Trends in Cognitive Science[12], which surveys the state-of-the-art of our current understanding, much of which has arisen from our own research. In particular, we have published a study using magnetoencephalography to demonstrate for the first time early (100–200 ms) differences in neural responses to infant and adult cry vocalizations in auditory, emotional, and motor cortical brain regions[13]. This early differential activity extends and complements our highly-cited discovery of a rapid specialized activity in response to infant faces[14] and may help to rapidly identify infant cries and engage affective and motor neural circuitry to promote adaptive behavioral responding, before conscious awareness. These differences were observed in adults who were not yet parents, perhaps indicative of a universal brain-based “caregiving instinct” but also providing further impetus to our ongoing longitudinal and cross-sectional scanning studies of parents.

We have further developed, tested and validated new behavioural tools for testing infant sensitivity in adults, both non-parents and parents. We have published a unique public available OxVoc database of infant and adult emotional vocalisations[15]. We have further validated this database in a large sample of 562 participants, where we demonstrate that adults can reliably categorize these sounds (as ‘positive,’ ‘negative,’ or ‘sounds with no emotion’), and rate valence in these sounds consistently over time[16]. In an extended sample of 945 participants (including the initial sample), we also investigated a number of individual difference factors in relation to valence ratings of these vocalizations. The results demonstrated small but significant effects of symptoms of depression and anxiety with more negative ratings of adult neutral vocalizations. In addition we found gender differences in perceived valence such that female listeners rated adult neutral vocalizations more positively and infant cry vocalizations more negatively than male listeners. Of note, we did not find evidence of negativity bias among other affective vocalizations or gender differences in perceived valence of adult laughter, adult cries, infant laughter, or infant neutral vocalizations. Together, these findings largely converge with factors previously shown to impact processing of emotional facial expressions, suggesting a modality-independent impact of depression, anxiety, and listener gender, particularly among vocalizations with more ambiguous valence.

Conclusion

Overall, combining careful experimental methods using music combined with state-of-the-art causal whole-brain modelling can perhaps for the first time reveal the brain mechanisms for any form of brain processing including that of music, opening up for new treatments; perhaps even eudaimonia and better lives - especially if coupled with early interventions.

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FACTS

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Selected ongoing research projects:

- Kringelbach M.L., Stark E.A., Alexander C., Bornstein M.H. & Stein A.: On cuteness: Unlocking the parental brain and beyond.
- Deco G. & Kringelbach M.L. : Metastability and coherence: Extending the communication-through-coherence hypothesis from a whole-brain computational perspective.
- Kringelbach M.L. & Rapuano K. : Time in the orbitofrontal cortex
- Chan RCK & Kringelbach M.L. : At Risk for Neuropsychiatric Disorders: An Affective Neuroscience Approach to Understanding the Spectrum.
- Fjaeldstad A., Fernandes H.M., van Hartevelt T.J., Gleesborg C., Møller A., Ovesen T. & Kringelbach M.L. : Brain fingerprints of olfaction: a novel structural method for assessing olfactory cortical networks in health and disease.
- Witek M. A. G., Popescu T., Clarke E., Hansen M., Konvalinka I., Kringelbach M.L. & Vuust P. : Effects of syncopation on free body-movement in groove music.
- Parsons C.E., Young K.S., Jegindø E.-M., Stein A. & Kringelbach M.L.: Interpreting infant emotion expressions: parenthood has differential effects on men and women.

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MUSIC IN THE BRAIN

by Peter Vuust

The Danish National Research Foundation's Center for Music in the Brain (MIB) was officially opened 5 June, 2015, with a grand ceremony in the Concert Hall, Aarhus. This celebration featured performances by the prize-winning Swedish piano player Lars Jansson, the Cello Ensemble of the Royal Academy of Music Aarhus/Aalborg (RAMA), a lecture and musical performance by neurologist and flautist, Professor Eckart Altenmüller from Hannover and speeches by Liselotte Højgaard, Chairman of the board of the Danish National Research Foundation, Brian Bech Nielsen, rector of Aarhus University (AU), Claus Olesen, principal of the Royal Academy of Music, Aarhus/Aalborg (RAMA) and Peter Vuust, director of MIB.

MIB is based on four strands of research in music and the brain, each led by acclaimed international experts: **Perception**, led by Professor Lauren Stewart: centered around music perception and cognition, **Action**, led by Professor Peter Vuust: centered around the processing of musical rhythms and the interaction between rhythm and motor behaviour, **Emotion**, led by Professor Morten Kringelbach: centered around the relationship between music and emotions, and how and why music brings pleasure, and **Learning**, led by Professor Elvira Brattico: centered around the effect of music training, expertise and individual traits. Even though distinct in their research goals, the four groups are unified by the common framework of the predictive coding of music theory ensuring a number of mutual collaborations between the four groups as testified by several joint publications in 2015.

The centre is situated uniquely between the musical excellence of RAMA, and the outstanding neuroscientific facilities at the Center of Functionally Integrative Neuroscience (CFIN), under the Department of Clinical Medicine at AU. It is physically located with offices at the Danish Neuroscience Center and has direct access to stateof-the-art brain scanning technologies such as PET, MRI, fMRI, MEG, EEG, tDCS, and TMS.

MIB is off to an excellent start. During the first half year we have established ourselves with a core group of senior and junior researchers and an extremely experienced administrative staff. We have hired former leader of the administration of the Department of Clinical Medicine, AU, Tina Bach Aaen as centre manager, research secretary Hella Storgaard Kastbjerg, and student worker Signe Hagner. This small administration is integrated into the existing CFIN administration, which allows for MIB to draw on additional resources for fundraising and research dissemination. The administration has successfully implemented a number of administrative procedures for MIB and been responsible for managing the many new appointments at MIB.

MIB has been able to attract researchers from all parts of the world. PI Elvira Brattico has moved to Aarhus from Helsinki with her family, Morten Kringelbach and Lauren Stewart are partly situated in Oxford/London, partly in Aarhus, and bring a number of international students and researchers for shorter and longer research stays. Morten Kringelbach has brought his large ERC CAREGIVING grant and three postdoc researchers: Tim van Hartevelt (the Netherlands), Henrique Fernandes (Portugal) and Joana Cabral (Portugal). This project aims to understand the development of the parental brain and synergizes on many levels with the aims of MIB. We have hired Christine Parsons, formerly at Oxford University, as assistant professor and employed Maria Witek and Bjørn Petersen in assistant professorship positions. We also jointly chose Boris Kleber, formerly at Tübingen University, among 20 candidates for a postdoc/assistant professor position.

MIBs first half year has focused on attracting excellent young researchers and starting up new projects and collaborations. In the spring of 2015, we advertised internationally for four PhD positions using open calls within the field of music and brain. We had 39 applicants for the PhD positions and the four PIs jointly agreed to hire Maria Celeste Fasano (Italy), Patricia Alves da Mota (Portugal), Ole Adrian Heggli (Norway) and Suzi Ross (Scotland). We then assigned them to the four groups of the centre, where they each developed PhD project plans supervised by two or more of the PIs, and subsequently they were all accepted for admission at the Graduate School of Health, AU, starting December 1st, 2015. This procedure ensures the employment of the best possible international candidates and spurs collaboration and synergy between the four MIB groups. In addition to these recruitments, we obtained full funding for an additional PhD position for Stine Derdau Sørensen from the research committee of the Ministry of Culture, RAMA and the Graduate School of Health, AU, as well as funding for additional costs from TrygFonden, who also supports Kira Vibe Jespersen's PhD project. We also obtained 1/3 stipend from the Graduate School of Health, AU for Suzi Ross.

This internationalization of the MIB centre has further been strengthened by the talks given by the many international guest speakers at our seminars: http://musicinthebrain.au.dk/newsevents/news-archive They fertilize new research collaborations and enrich the research education.

To benefit optimally from these visits we have created a routine where the invited speakers attend speed talks given by MIB researchers allowing them to give expert feedback on their projects. The interest we have witnessed from international visitors supports MIB's aim to become a global hub for interdisciplinary research in music and neuroscience.

Supported by the long term funding from DNRF, the co-funding from the Department of Clinical Medicine at Aarhus University, Central Denmark Region, The Royal Academy of Music Aarhus/Aalborg, Aarhus University and our other generous funding sources, MIB sets out to fulfill the dual aim of understanding the questions of how music is processed in the brain and how this can inform our understanding of fundamental principles behind brain processing in general. Embedded in the strong environment at CFIN, a strong foundation in music practice and theory at the highest level, and a focus on clinical application of music, MIB will combine neuroscientific, musicological and psychological research in music perception, action, emotion and learning, to test the most prominent theories of brain function, and to influence the way we play, teach, use, and listen to music.

MIB retreat 2016 at Vadstrup 1771, Samsø, 22-24 August 2016.
Photo: Ole Adrian Heggli

FACTS

MIB Center members and collaborators:

- Peter Vuust
- Elvira Brattico
- Lauren Stewart
- Morten Kringelbach
- Bjørn Petersen
- Boris Alexander Kleber
- Christine Parsons
- Line Gebauer
- Henrique Fernandes
- Joana Cabral
- Maria Witek
- Tim van Hartevelt
- Cecilie Møller
- David Ricardo Quiroga Martinez
- Kira Vibe Jespersen
- Maria Celeste Fasano
- Niels Christian Hansen
- Niels Trusbak Haumann
- Ole Adrian Heggli
- Suzi Ross
- Patricia Alves da Mota
- Rebeka Bodak
- Stine Derdau Sørensen
- Hella Kastbjerg
- Signe Nybo Hagner
- Tina Bach Aaen
- Risto Näätänen
- Petri Toiviainen
- Eus Van Sommeren
- Marcus Pierce
- Krista Hyde
- Anders Dohn
- Eduardo A. Garza Villarreal
- Ivana Konvalinka

Predictive Coding of Music

The MIB research is centered around the Predictive Coding of Music hypothesis (PCM) formulated by Peter Vuust and colleagues in 2009.

PCM states that music, based on the concept of anticipation, reflects fundamental survival-related brain mechanisms associated with predicting future events and has been demonstrated in relation to auditory pre-attentive processing and to processing of musical pleasure in the dopaminergic pathways. PCM ties musical anticipatory processes to emerging theories that posits predictive coding as the general principle underlying brain function in general.

It is our hope that this effort will significantly influence our understanding of brain function and plasticity, with implications for music education and clinical applications of music.

MUSIC IN THE BRAIN

Oxytocin improves prediction in social interaction

by Line Gebauer, Maria Witek, Niels Chr. Hansen, Jana Thomas, Ivana Konvalinka, and Peter Vuust

The ability to predict the behaviour, thoughts and feelings of others is essential for successful social interaction[1]. The more similar other people are to oneself, the easier it is to simulate their state, leading to more successful predictions[2]. Online prediction[3] and adaptive error correction[4] are also fundamental to synchronisation, since accurate alignment of movements requires the projection of future events based on past events and continuous motor adjustments. It is therefore not surprising that synchronisation increases interpersonal liking[5].

In recent years, the neuropeptide oxytocin (OT) has received extensive interest in social neuroscience due to its effects on social bonding[6] and trust[7]. OT is often referred to as a 'social hormone' and has been suggested to *directly* improve higher order social cognition. Alternatively, OT has been suggested to enhance social behaviours *via* a reduction in stress and/or anxiety[8]. Here we put forth the alternative hypothesis that OT affects social interaction by facilitating interpersonal synchronisation via prediction.

Adopting an interpersonal tapping paradigm as a model of minimal social interaction[3], this study looked at the relation between OT and interpersonal synchronisation. Dyads were administered either OT (n = 50) or a non-active placebo intranasally (n = 48). Both dyad members always received the same solution and were seated in two separate closed-off rooms with headphones through which auditory feedback was provided. They were instructed to tap along to a beat on Yamaha piano keyboards in three conditions varying in degree of social interaction (see Figure 1): 1) computer condition/non-social tapping (both only hear regular computer-generated beats); 2) bidirectional coupling/tapping to responsive other (both participants hear beats generated by the other participant, but not their own tapping); and 3) unidirectional coupling/tapping to unresponsive other (both participants hear only tapping of either member one or member two; e.g. member one taps to self while member two taps to member one, causing a leader-follower relationship). From the recorded MIDI data, we extracted measures such as the synchronisation index (SI), calculated as variance of relative phase; tapping variability, calculated as standard deviation (SD) of intertap-intervals (ITIs); and amount of positive and negative asynchrony, indicating whether tappers reacted to or anticipated the other's tapping. Questionnaires recorded mood and liking of tapping partner.

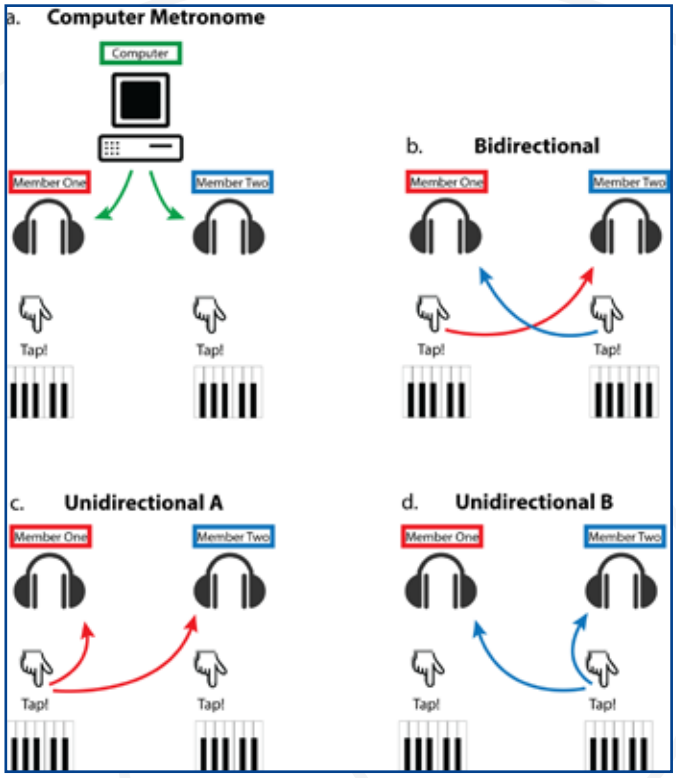

Figure 1
Tapping conditions with different degrees of social interaction: (a) computer condition/non-social condition where both dyad members hear and tap to regular computer generated beats; (b) bidirectional coupling/tapping to responsive other where both participants hear and tap to beats generated by the other participant, but not their own tapping; (c-d) unidirectional coupling/tapping to non-responsive other where both participants hear and tap to only the tapping of either member one (c) or member two (d), causing a leader-follower relationship. Auditory feedback is indicated with arrows. Green indicates the computer, red indicates member one, and blue member two.

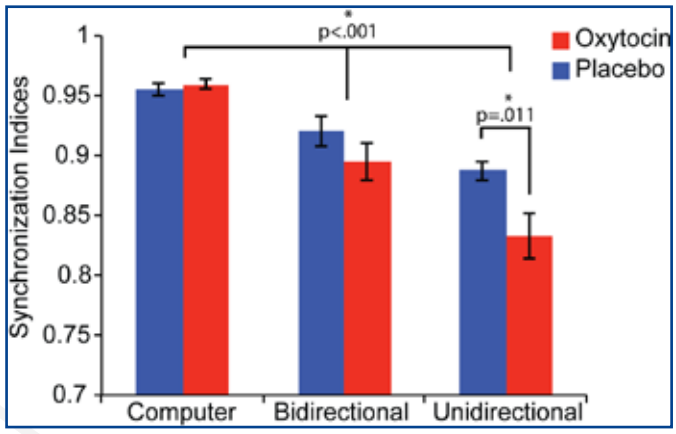

Figure 2
Effect of oxytocin vs. placebo on synchronisation indices during tapping to computer, bidirectional and unidirectional tapping. * indicates a significant contrast at p < .05 Error bars represent standard error of the mean.

We hypothesized that there would be an interaction between group and social condition, i.e. that dyads given OT would show increased synchronisation and decreased tapping variability compared to dyads given placebo, but only in social conditions. We also expected to see more anticipatory rather than reactive tapping in the OT group.

For synchronisation indices (SI), our results showed that overall, participants in both groups were most synchronised in the computer condition, followed by the bidirectional and unidirectional conditions, respectively (see Figure 2). More interestingly, there was a significant interaction between group and condition, indicating that the OT group synchronised significantly better than the placebo group in the unidirectional condition, but there were no significant effects of OT in the bidirectional and computer conditions. These results suggest that oxytocin makes people more synchronised, but only in conditions where one tapper is leading and the other following. For tapping variability (SD of ITIs), we found no significant group difference in the computer or bidirectional conditions. In the unidirectional condition, we split the groups into 'leading' (tap to self) and 'following' (tap to unresponsive other), and here we found a significant interaction between role (leading, following) and group (oxytocin, placebo). Figure 3a shows that the difference in variability between leading and following was greater in the placebo group than the OT group. This means that, when controlling for self-paced leading variability, followers given OT were less variable than followers given placebo. This reduced temporal variability caused by oxytocin could explain the overall improved synchronisation that we found between tappers. Figures 3b and 3c exemplify tapping variability of followers and leaders in single dyads of the oxytocin and placebo groups, respectively.

For asynchronies during unidirectional tapping, there was no group difference in negative asynchronies, but OT tappers produced significantly lower positive asynchronies than placebo tappers. Furthermore, while for the OT group there

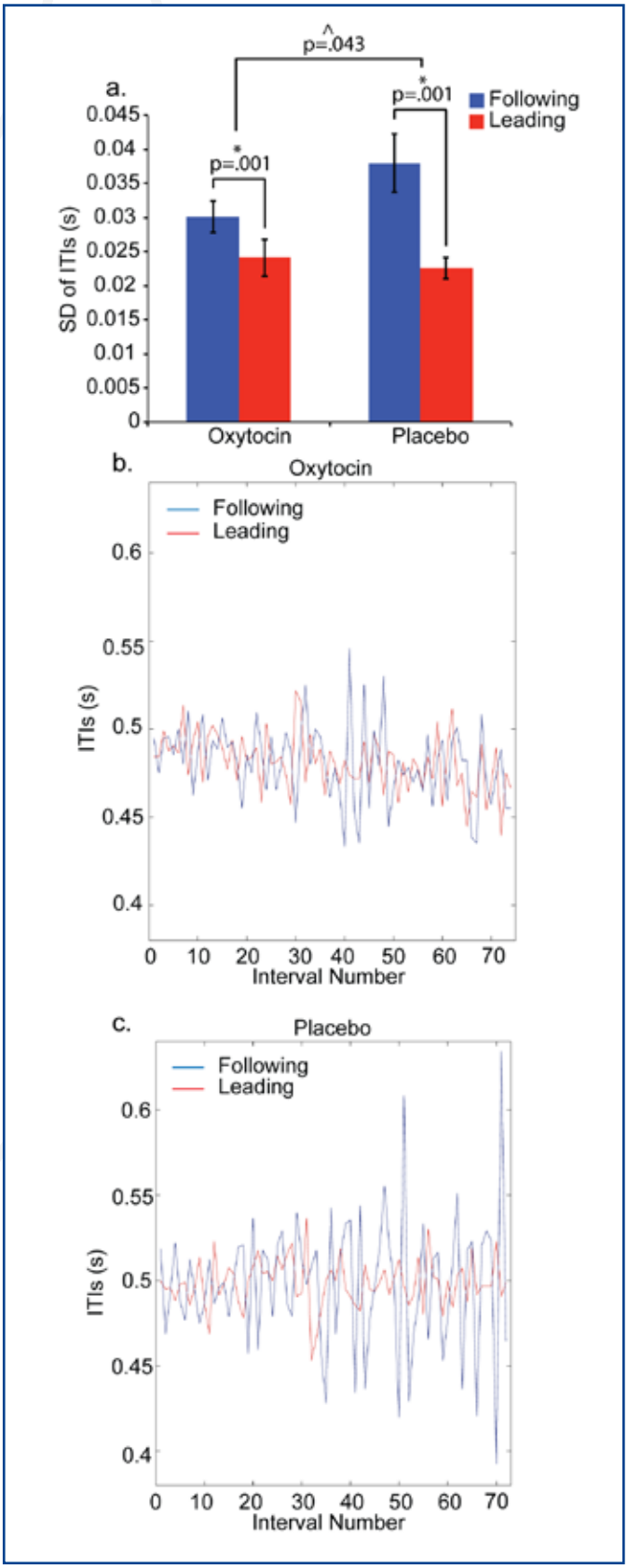

Figure 3

Effect of oxytocin vs. placebo on tapping variability. (a) Standard deviation (SD) of inter-tap intervals (ITI) for leading (tap to self) and following (tap to unresponsive other) during unidirectional tapping. * indicates a significant contrast $p < .05$. ^ indicates a significant interaction at $p < .05$. Error bars represent standard error of the mean. (b) Example of tapping dyad given oxytocin during unidirectional tapping, showing reduced following variability. (c) Example of dyad given placebo during unidirectional tapping, showing greater following variability.

were negative correlations between synchronisation indices and both positive and negative asynchronies, there was only a negative correlation between SIs and positive asynchronies for the placebo group. Together, these results suggest that without the added oxytocin, participants more frequently lagged behind as opposed to anticipated their tapping targets. No effect of OT was found on mood or liking of tapping partner.

To summarise, we show for the first time, using an interactive finger-tapping paradigm, that OT improves prediction in interpersonal synchronisation. The effect of OT on synchronisation and temporal variability suggests that OT improves the ability of a follower to anticipate the tapping of an unresponsive leader. Furthermore, a reduction in positive asynchronies, as we see for our OT group, has previously been associated with less reactive and more anticipatory behaviour[9].

Despite OT being repeatedly shown to affect subjective reports of pro-social attitudes, we did not find a significant effect of OT on liking of tapping partner. Thus, our data indicate that rather than having a direct effect on specialized higher-order social behaviour, OT primarily affects low-level behavioural interaction outside the participants' conscious awareness, i.e. their ability to follow and predict the taps of an unresponsive partner. We suggest that this effect may mediate pro-social attitudes[7]. Another mechanism that has been suggested to mediate pro-social effects of OT is anxiety and stress reduction[10]. We did not find a significant change in mood, neither in the OT nor the placebo group. Thus, our findings do not suggest that anxiety reduction is the primary mediator of the pro-social effects of OT. Nor do we have evidence that anxiety should affect sensorimotor synchronisation. This supports our suggestion that the primary effect of OT is on interpersonal sensorimotor prediction, temporal variability and synchronisation itself. We thus contribute to the on-going debate regarding the mechanism behind oxytocin's pro-social effects, and highlight the importance of prediction in social interaction more broadly.

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NEW FACES at CFIN & MIB

In 2015 the first four PhD students at Center for Music in the Brain was hired to perform PhD projects within the four strands of MIB research: perception, action, emotion and learning.

From left to right: **Maria Celeste Fasano** from Italy investigating: *Brain changes after multimodal learning: a behavioral and neuroimaging study on music training in early adolescents*, **Ole Adrian Heggli** from Norway working with: *Neural and behavioural interpersonal coordination mechanisms*, **Patricia Alves da Mota** from Portugal doing a project on: *Music, pleasure and creativity: Modelling the functional architecture of the human brain under stimulation with music*, and **Suzi Ross** from Scotland working on: *Pitch prediction in expert musicians*.




They are all four well on the way now, collecting data for their projects.

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NEW FACE at CFIN & MIB

Boris Kleber, PhD, Assistant Professor, Department of Clinical Medicine, Aarhus University.

Born into a family of professional artists (piano, violin, voice, dance, and composition), Boris grew up in an environment of opera and classical music. Following his high-school graduation at a music profile school, he first studied contemporary dance and dance pedagogy at the Tanzwerkstatt Konstanz (Graduate Diploma in 1995) and continued private lessons in classical guitar and music theory.

Boris completed a Master of Science (2002) in psychology at the University of Konstanz (Germany), received a PhD in Neuroscience (2009) from the University of Tübingen (Germany), and was awarded a higher doctorate degree (Habilitation) in Psychology from the University of Tübingen (2016).

His scientific interest and passion for the singing voice is strongly influenced by his early musical experiences. An internship at the Lichtenberg Institute for Functional Voice Training in 1997 deepened his understanding of voice physiology, which motivated the development of his master's thesis in psychology, focusing on aesthetic perception of classical singing voices. A specialization in Clinical Psychology involved psychogenic voice disorders and musical performance anxiety. Post-graduate collaboration with Professor John Gruzelier (Imperial College/ Goldsmiths - University of London) and Professor Aaron Williamon (Royal College of Music, London) finally fuelled his desire to perform research in the neurosciences of music.

This path involved several intermediate positions during which he was involved with Mismatch Negativity and Brain Computer Interface research, before Boris was awarded a self-authored PhD grant from the German Research Foundation, supervised by Professor Niels Birbaumer and Professor Martin Lotze at the Institute for Medical Psychology (University of Tübingen). During his PhD, he worked with EEG Neurofeedback and pioneered fMRI research with trained singers as a model for experience-dependent plasticity of the vocal motor system. This work was crucially developed during his post-doctoral research with Professor Robert Zatorre at the Montreal Neurological Institute (QC, Canada). When he returned for a faculty position to the Institute for Medical Psychology (University of Tübingen), he gained substantial experience in TMS and real-time fMRI neurofeedback as well as in teaching Psychology and Medical Psychology at the Medical Clinic and the Department of Psychology.

At the Center for Music in the Brain, Boris integrates his previous work on vocal motor control in trained singers with the concept of predictive coding. This combination presents a new line of research in the speech motor domain. Singing furthermore allows investigating sensorimotor interactions without the necessity of building MRI compatible musical instruments. The basic knowledge of audio-motor and somatosensory-motor transformations in the context of vocal learning may also have significant ramifications for clinical applications in vocal production disorders.

CNRU

2015 & 2016

by Mads Jensen, Martin Dietz, Kristian Sandberg & Morten Overgaard

Cognitive Neuroscience Research Unit, CNRU, is an interdisciplinary research group, performing experimental and theoretical research within cognitive neuroscience, neurorehabilitation, and philosophy of mind and science. For CNRU it is a fundamental ideology that the interdisciplinary cooperation between basic science, clinical research and philosophy is reflected in all research projects.

Human consciousness can be defined as the inner subjective experience of mental states such as perceptions, judgments, thoughts, intentions to act, feelings or desires – all of which are observable from a first person perspective only. Cognitive neuroscience is however classically conceived as a science of behaviour and brain – i.e. what can be observed from a third person perspective. Although this fundamental difference in perspective makes a scientific approach to consciousness highly methodologically challenging, CNRU researchers attempt to approach the question from different angles. Over the last years, most work has focussed on exploring the neural correlates of conscious perception – how this relation should be generally conceived and how individual differences can be explored – the understanding volition and agency, and clinical applications in psychiatry and neurology.

Consciousness and neural correlates

Much recent debate in consciousness research has centered on the neural correlates of consciousness – in particular whether consciousness should be associated with prefrontal or sensory regions in the brain. The question is difficult as sensory regions are easily confounded with processes occuring prior to consciously experiencing a perception, whereas prefrontal regions are easily confounded with processes occuring after.

However, even though this debate is very central to consciousness research, it seems unclear how an answer will be an answer to the fundamental question that motivated consciousness research to begin with: Why are any specific neural activations associated with consciousnes at all? How can there even exist a “first person perspective”?

Over the last years, parts of CNRU research activities have centered on how to relate theories of consciousness more directly to experimental investigations. This work has led to the creation of the theoretical framework REF-CON, from the perspective of which the relation between brain function and brain structure is better understood.

In current scientific literature, one still sometimes encounters the view that particular brain functions “are” particular brain regions even though functions (e.g. cognitive functions) seemingly can be the same between individuals with very different brains (e.g. brain injured persons or just individual differences). At the same time, other views suggest that functions should be understood as “computation” only – i.e. that the underlying biological substrate is of little or no significance. We believe that a main interest for neuroscience should be to develop models from the perspective of which such paradoxes and unsolvable mysteries (including the “mystery” of consciousness) do not appear.

Individual differences in conscious perception

Statistical explanation of individual variability in cognitive characteristics from neural measures obtained using MRI is becoming an increasingly large subfield of cognitive neuroscience for a number of reasons. One main reason is that it is financially and logistically advantageous that the same (expensive) MR data set can be related to a high number of behavioural measures. Potential statistical issues related to multiple comparisons are handled easily as the number of corrections that can be made at a certain effect size and power level increases exponentially as a function of sample size. In other words, one study correlating two behavioural variables with a set of neural variables has greater power than two studies, each with half the sample size, correlating a single behavioural variable with a set of neural variables.

With this in mind, it is not surprising that many laboratories across the world conduct larger studies than previously. These large MRI data sets are useful not only for examining new hypotheses, but may also easily be used for replication

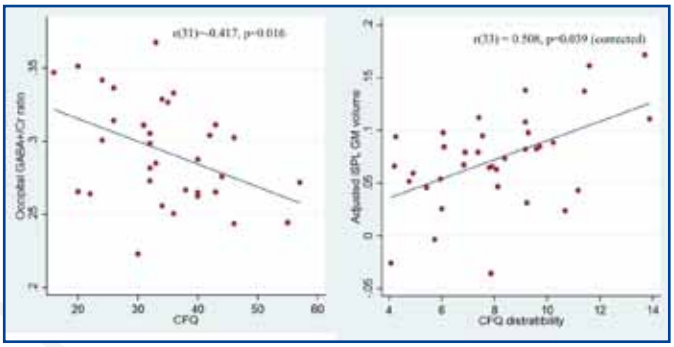


Figure 1
Neural correlates of cognitive failures. Left: Correlation between cognitive failures questionnaire (CFQ) scores and occipital GABA/Cr ratio. Right: Correlation between CFQ distractibility scores and adjusted left superior parietal lobule grey matter volume.

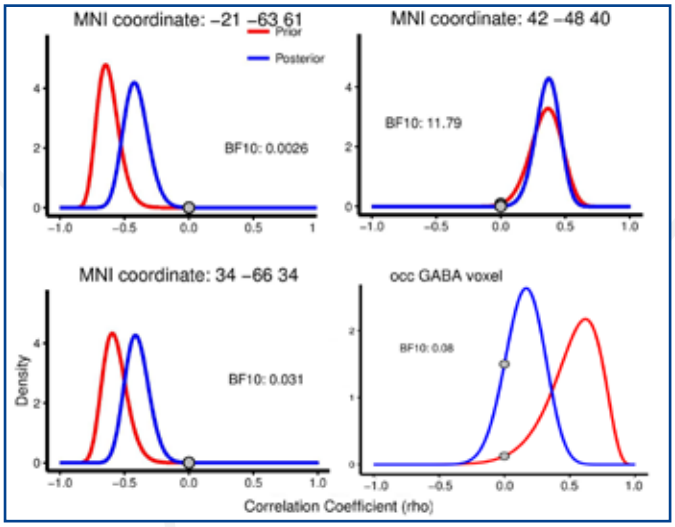


Figure 2
Replication results. Percept duration in an ambiguous perception paradigm, structure-from-motion, has been related to occipital GABA concentration[3] as well as GM volume in a number of parietal areas[4–6]. Here we report the results of a Bayesian replication analysis basing the prior distributions on the correlation coefficient and number of participants in the previous studies. Distributions are plotted for three parietal coordinates and for occipital GABA/Cr. Grey dots indicate the probability density at rho = 0 (i.e., the likelihood of no correlation) for each curve. Evidence against the null was found only at a coordinate in the right aSPL (MNI coordinates [42 -48 40]).

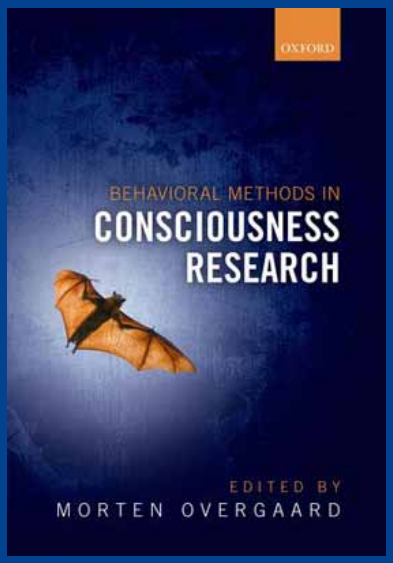
attempts. Over the last few years, we have published a handful of magnetic resonance spectroscopy (MRS) studies with what was at the time a large sample size for that type of study, and we are currently starting up a much larger project in which we aim to scan hundreds of normal, healthy individuals as well as brain injury patients using a wide range of MR protocols.

In one study on the neural correlates of the propensity for cognitive failures in daily life (measured by the cognitive failures questionnaire), we examined two parts of the system involved in visual attention: the superior parietal lobule (believed to be involved in top-down modulation) and the visual cortex (in which lateral, inhibitory connections may play a role). First, we found that cognitive failures were negatively correlated with occipital GABA/Cr ratio (obtained using MRS) (Figure 1). Next, we replicated a previous finding linking the distractibility component of cognitive failures to grey matter volume in a specific area of the left superior parietal lobule (SPL) (Figure 1), and finally we established that grey matter volume of this area also correlated with the overall CFQ score. Interestingly, the two neural measures were uncorrelated, and thus contributed independently of each other to the statistical explanation of cognitive failures. A possible explanation for the results is that GABA in sensory areas reflect the potential capacity to selectively suppress irrelevant information, and that such suppression can be controlled in part from the SPL.

In a second study examining similar parts of the visual system, we attempted to replicate two previous sets of findings about the neural correlates of the dynamics of alternations of perception during viewing of a visually ambiguous stimulus (a structure-from-motion paradigm). Specifically, previous studies had found that the mean percept duration (i.e. the time until an alternation occurred) was related to GABA/Cr ratio in the occipital cortex as well as the grey matter volume of a number of parietal areas. Analyses were conducted within a Bayesian framework, and support for the null was found for most analyses (Figure 2). Overall, the results supported the relationship between percept duration and the grey matter volume of the right anterior SPL whereas correlations between percept duration and other parietal areas as well as occipital

Behavioural Methods in Consciousness Research

In 2015, Morten Overgaard's book Behavioural Methods in Consciousness Research was published. The book provides an overview of methods and approaches for studying consciousness and thus sums up important aspects of the work of the CNRU group over the last years. The book aims to stimulate progress in this field by giving concrete tools for investigating consciousness as well as theoretical discussions of possibilities and limitations of each method.



GABA were not directly replicated. Nevertheless, models including grey matter volume of 3 peak coordinates in the parietal lobe explained 33% of the inter-individual variability in percept duration, showing that although the relationships were not as strong as previous studies reported, the parietal lobe likely plays a large role in determining the duration with which a perceptual interpretation is kept stable under ambiguous viewing conditions, or perhaps more generally the process of making representations conscious through selective amplification/suppression.

Volition and action

A part of the work in CNRU has been about measuring and investigating intentions, especially in relation to the conscious experience we have of performing voluntary actions and movements. In a series of experiments, we have tried to investigate how the separation of the creation of intentions-to-act from the actual movements affect the experience of actions. These experiments showed that the time between the creation of intention to the action is executed affect the experience of control we have over that action.

In a series of experiments using Magnetoencephalography (MEG), we investigate if it is possible to separate the neural signals of intentions from neural signals affiliated with motor components, e.g. planning and movements. Extending on our previous experiments, we investigate how the functional network properties of creating intentions-to-act is different from implementing intentions-to-act – i.e. executing actual movements.

The methodological challenges related to the study of intention and experience of action is, however, surprisingly often overlooked. Whereas the measure of perceptual consciousness is historically difficult (given its subjective nature), it is possibly even more difficult to study intentions and volition that are not directly related to an objective stimulus. Nevertheless, inspired by methods we have previously developed to study perceptual consciousness, we have tested a scale based on the participants' own introspective descriptions to measure the experience of control related to movements. The scale (the Control Awareness Scale, or CAS) will be employed in future experiments when more fine-grained information about the subjective side of controlled movements is desired.

Computational neurology

In later years, we have worked to use highly sensitive measurements at all levels of description – neuroimaging techniques as well measures of mental states.
Over the past years, electrophysiological techniques (MEG and EEG) have assumed a more and more central role in both cognitive and clinical brain experiments at the CFIN. In one experiment, we have used Bayesian analysis of effective connectivity to investigate neglect as a dysconnection syndrome. In this study, we show that healthy controls use a right-dominant cortical network composed of hierarchically organized parietal, frontal and temporal regions. This finding replicates our previous finding in the young adult brain using the same experimental paradigm. We were then able to

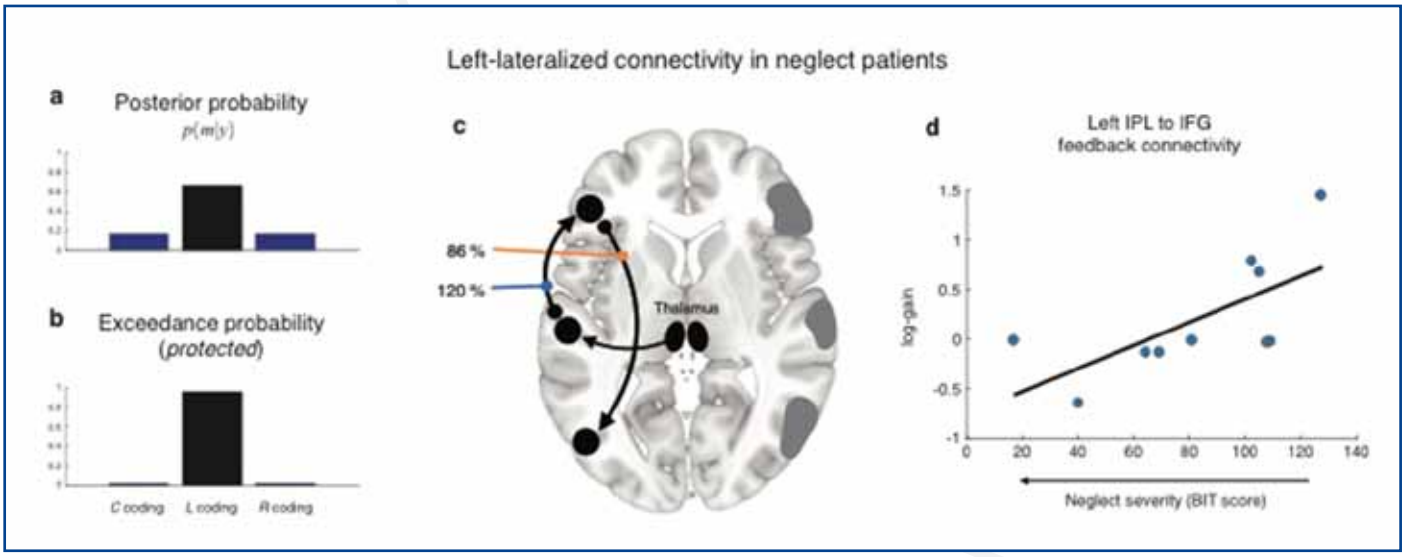


Figure 3
Left-lateralised connectivity in neglect patients

show that neglect patients have a dysconnection between parietal and frontal cortex in the right hemisphere when stimuli appeared on their neglected side, but preserved connectivity in the left hemisphere when stimuli appeared on their right. Crucially, this right parieto-frontal connectivity decreased as neglect severity increased. This points to neglect as a dysconnection syndrome that is consistent with a failure of predictive coding of the sensorium.

In a long-term collaboration with the Department of Neurosurgery and Hammel Neurorehabilitation and Research Center, we have used EEG to record cortical responses from patients with a disorder of consciousness (DoC). Following an acute period of coma, DoC patients are typically divided into one of two categories: the vegetative state or the minimally conscious state. Currently, the two key determinants in this differential diagnosis are the patient's level of arousal and whether his or her motor behaviour is believed to be voluntary or simply reflexive. This means that we have to infer any dysfunction of the neurophysiological mechanisms that mediate perception of the external world by comparison to the healthy brain. In this study, we have used Bayesian model selection to address the problem of selecting an optimal model among a set of alternative hypotheses about how patients are classified, given their electrophysiological responses. By formally comparing a set of alternative hypotheses about how patients are grouped, we are able to show that patients in the vegetative state and minimally conscious patients are best explained as one joint class. In other words, there is no discernible difference in the MMN response between these patients as diagnosed according to the Coma Recovery Scale – revised. We therefore propose that electrophysiological responses, recorded non-invasively, will become a valuable complement to behavioural diagnostics in the classification of DoC patients. This article is being submitted for peer review.

In a series of experiments, we have investigated how hallucinations in schizophrenia work. In one experiment, we showed that patients with schizophrenia have the same ability to discriminate between perceptual stimuli as healthy participants. Unlike healthy individuals, however, patients with schizophrenia showed poor match between reports of subjective clarity and discrimination ability. In other words, in schizophrenia, there is less correlation between reports of subjective experience and perceptual performance than in a healthy population, indicating that schizophrenia may involve disturbed higher order cognition to a higher degree than first order perception.

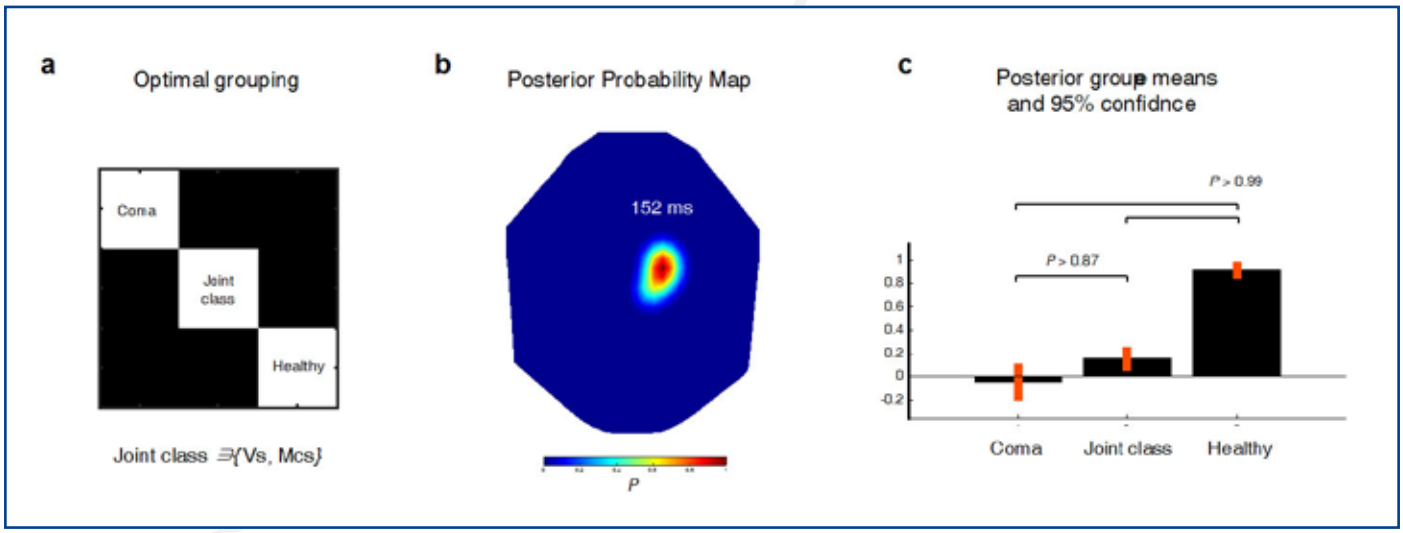


Figure 4
Optimal grouping patients with a disorder of consciousness, given their electrophysiological data

Highlights in 2015 & 2016

DHL Relay Race 2016

As in previous years CFIN/MIND*Lab* and MIB people participated in the annual DHL Relay Race.

Thursday 18 August 2016 all Aarhus University teams and a lot of other company teams filled 'Mindeparken' close to Marselisborg Castle and had a great evening.

In 2016 CFIN/MIND*Lab* and MIB had 5 running teams and 3 walking teams participating in the event, and as always some of the fast and experienced runners made great time.

Others are just there for a fun evening in the company of good collegues, and the DHL Relay Race is always popular, chaotic, fun, noisy, sweaty, ...

We will OF COURSE be back in the starting blocks, baton in hand and READY, next year.

Photos: AU Foto & Hella Kastbjerg

AWARD

Morten Overgaard receives the Young Scientist Award

In 2015, for the second year in a row, Morten Overgaard was awarded the Young Scientist Award by the World Economic Forum given to the 40 most outstanding scientists in the world under the age of 40. Morten received the award the first time in 2014 at the Annual Meeting of the New Champions that was organized by The World Economic Forum in Tianjin, China, in September 2014.

Danish Stroke Collaboration Symposium 2016

To create a forum for researchers within the stroke field in Denmark, the research groups at CFIN/MIND*Lab*, Aarhus University and Department of Neurobiology Research, University of Southern Denmark founded the Danish Stroke Collaboration.
The first Danish Stroke Collaboration Symposium took place 16-17 June 2016 in Aarhus initiating a series of future annual meetings. At these symposia stroke researchers within basic and clinical research can get together to present and discuss current stroke research and exchange knowledge. In addition, these meetings will present good opportunities to extend or start new collaborations.

At the first meeting at Aarhus University, presentations were given by several senior scientists as well as an invited keynote lecturer. As an opportunity for younger researchers to present their projects, the meeting included chaired poster sessions.

Talks by:

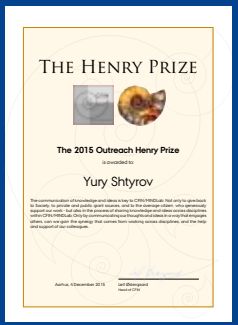
- Kate Lykke Lambertsen, Department of Neurobiology Research, SDU
- Anders Bach, Department of Drug Design and Pharmacology, KU
- Kim Ryun Drasbek, Center of Functionally Integrative Neuroscience, AU
- Zindy Raida, Scanbur
- Keynote lecture: Grethe Andersen, Danish Stroke Center, Dept. of Neurology, AUH
- Anne Nielsen, Center of Functionally Integrative Neuroscience, AU
- Bettina Hjelm Clausen, Department of Neurobiology Research, SDU
- Jens Nyengaard, Stereology and Electron Microscopy Laboratory, AU

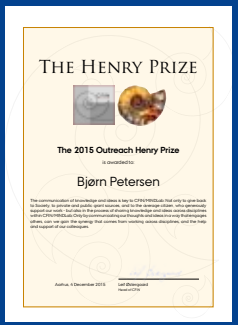
Danish Stroke Collaboration

The Henry Prize

The communication of knowledge and ideas is key to CFIN / MIND*Lab*'s mission: Not only to give back to Society, to private and public grant sources, and to the average citizen, who generously support our work - but also in the process of sharing knowledge and ideas across disciplines within CFIN / MIND*Lab*: Only by communicating our thoughts and ideas in a way that engages others, can we gain the synergy that comes from working across disciplines, and the help and support of our colleagues. To reward and acknowledge CFIN and MIB employees who make extraordinary efforts in these respects, everyone can nominate colleagues worthy of The Henry Prize.

The Henry Prize is awarded every year, during a ceremony taking place at the annual CFIN & MIB Christimas Dinner.
It constitutes 5000 DKK, to be used for work-related travel or equipment in the widest sense at the recipients discretion, provided that this activity/need is not currently funded from other sources.



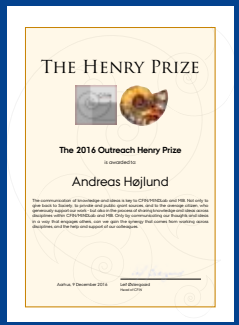


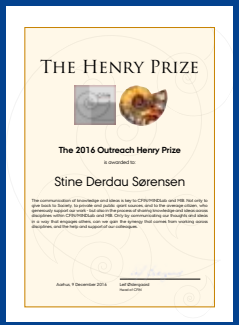
In **2015** The Henry Prize was awarded to:

- Yury Shtyrov (CFIN)
- Bjørn Petersen (MIB)

In **2016** The Henry Prize was awarded to:

- Andreas Højlund (CFIN)
- Stine Derdau Sørensen (MIB)





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2015 & 2016 Publications

Peer reviewed articles:

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